C012-H06113-15-P25 90
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January 1988 Vol. 72 No. 1

British Journal of
Ophthalmology

(15)

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H

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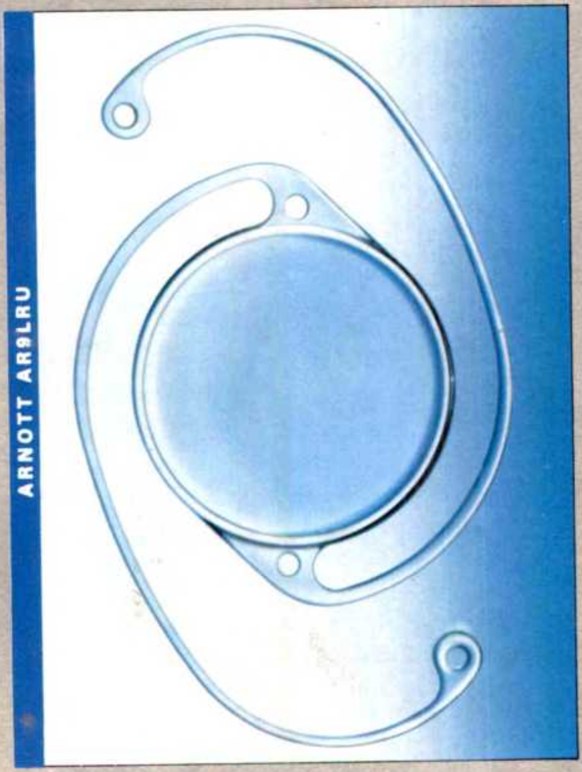

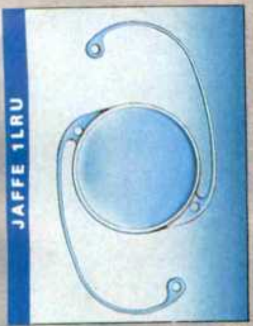

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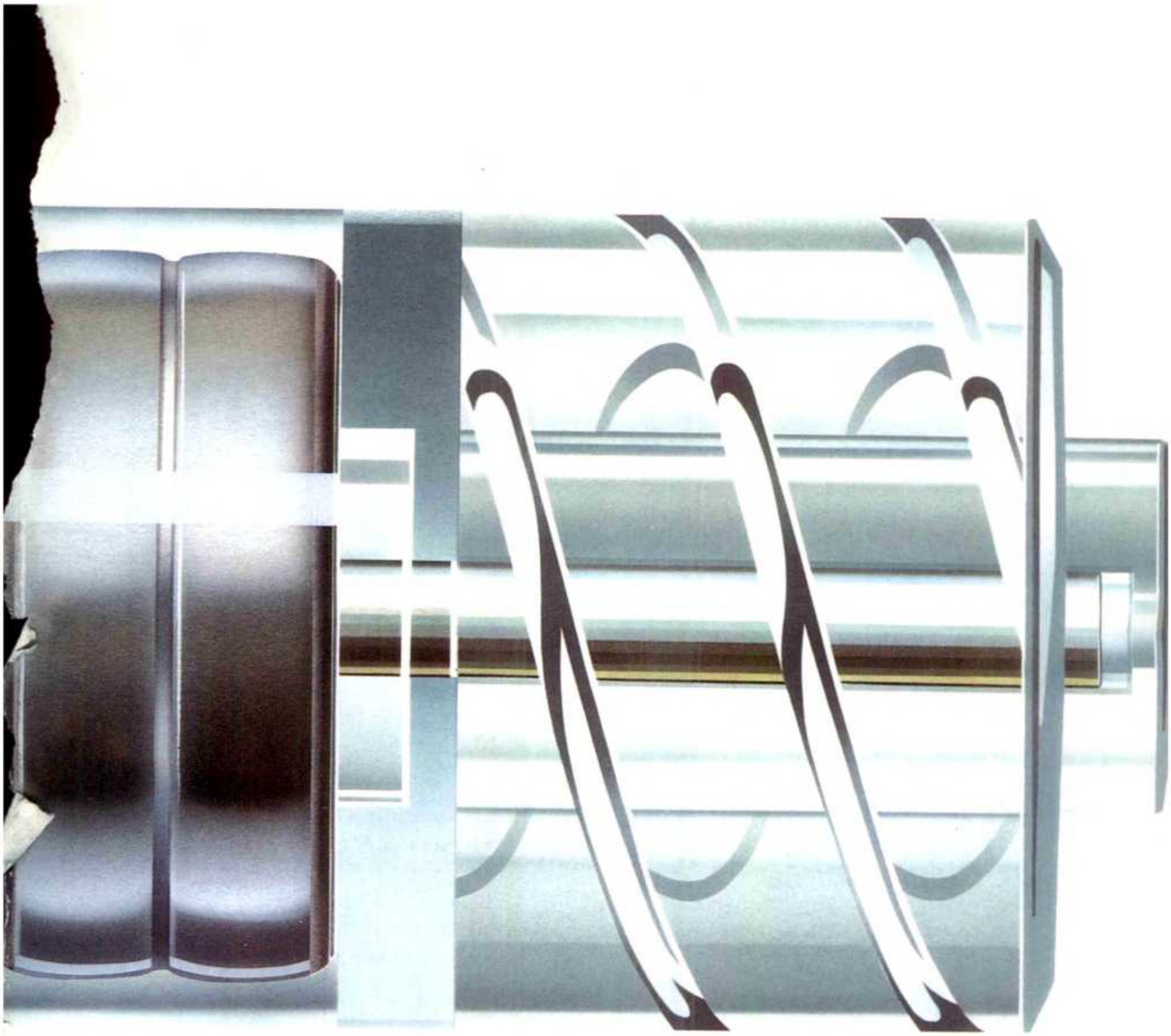

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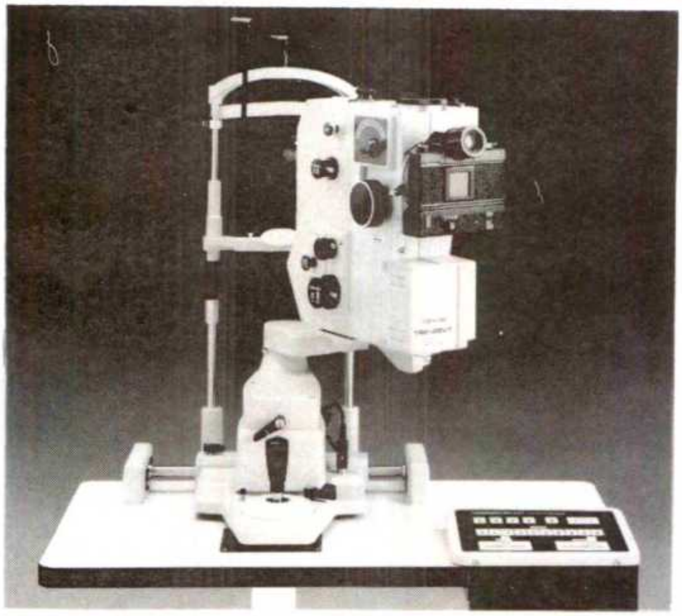

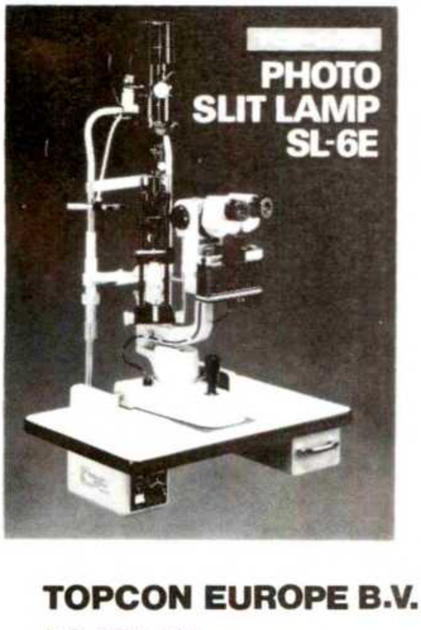

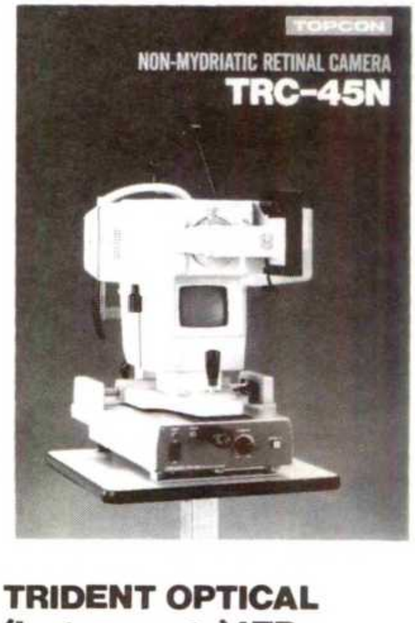

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Editorial: Why retrobulbar anaesthesia?

Having been asked if she would consent to a local anaesthetic for her cataract extraction a patient replied that she did not have complete confidence in the local doctors but would prefer a London man, preferably from Harley Street. However, when the matter was further explained, and the superior safety of local anaesthesia enlarged upon, she duly gave her consent.

Fortunately the optimistic prediction of the harmlessness of this type of anaesthetic proved to be accurate. But was she really informed? What if she had had a retrobulbar haemorrhage, an accidental perforation of the globe,[1] transitory blindness,[2] central retinal artery occlusion,[3] central retinal vein occlusion,[4] or a contralateral second and third cranial nerve dysfunction, as reported by Rodgers and Orellana in this issue? This particular patient's ophthalmologist (myself) would have had some explaining to do which, in view of the response to the initial questioning, could have been awkward.

The usual reason for choosing local anaesthesia in our hospital is because the patient is judged to be unfit for a general anaesthetic, but one is well aware that the choice of local or general anaesthesia varies from hospital to hospital and from country to country. However, when local anaesthesia is used for reasons of safety, it ought to be as safe as possible. Although Rodgers and Orellana rightly point out that retrobulbar anaesthesia is seldom associated with serious sequelae, nevertheless their case and others in the literature indicate that serious problems can and do occasionally occur. It is perhaps worth pointing out that it is almost as easy to carry out cataract extraction without a retrobulbar anaesthetic (or even a seventh nerve block), though most surgeons using a microscope believe (mistakenly) that there will be so much movement as to render the operation unduly hazardous. Let me assure readers that a few drops of amethocaine followed by 1 ml of subconjunctival 2% lignocaine injected under direct vision in the region of the superior rectus insertion are all that is required. This might be thought preferable to the alternative suggestion of a retrobulbar injection with a blunt needle as advocated by some authors.

If it does nothing else it at least removes the inconvenience and embarrassment of the inevitable occasional retrobulbar haemorrhage.

REDMOND J H SMITH

References

1 Lincoff H, Kreissig I. Local anaesthetic with accidental perforation of the eye—an acute emergency. *Klin Monatsbl Augenheilkd* 1986; 188: 128–32.

2 Marx P, Langlois J, Brasseur G. Transitory blindness after retrobulbar anaesthesia. *Bull Soc Ophtalmol Fr* 1979;79: 925–8.

3 Klein ML, Jampol LM, Condon PI, Rice TA, Serjeant GR. Central retinal artery occlusion without retro-bulbar haemorrhage after retro-bulbar anaesthesia. *Am J Ophthalmol* 1982; 93: 573–7.

4 Sullivan KL, Brown GC, Forman AR, Sergott RC, Flanagan JC. Retro-bulbar anaesthesia and retinal vascular destruction. *Ophthalmology* 1983; 90: 373–7.

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Increased procollagenase activating angiogenic factor in the vitreous humour of oxygen treated kittens

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SUMMARY Previous studies have demonstrated an increase in a low molecular weight angiogenic factor (ESAF) present in the retinae of kittens with oxygen induced retinopathy. The present paper describes differences in the quantity of ESAF extracted from the vitreous humour of control and oxygen treated animals and proposes a mechanism for the induction of intravitreal neovascularisation.

The existence of an angiogenic factor in retinal tissue undergoing active vascularisation was first proposed by Michaelson[1] in 1948. It was suggested that such a factor would be a small freely diffusible molecule,[2] the release of which could be brought about by hypoxia.[3-5] Release of such a factor into the vitreous humour and its accumulation therein would bring about the vascularisation of this tissue by retinal vessels.

Retinal extracts have been shown not only to promote angiogenesis in the cornea[6] and the chick chorioallantoic membrane[7] but also to contain a low molecular weight endothelial cell angiogenic factor (ESAF).[7,8] The quantitative assay of this molecule can be achieved by virtue of its ability to activate skin fibroblast procollagenase in a dose dependent manner,[9] and differences in the quantities of ESAF present in normal and oxygen treated retinae have already been described.[10] Other recent studies have shown ESAF to be present in vitreous humour taken from both normal eyes* and from those with proliferative diabetic retinopathy.† Hence it appears that in conditions of proliferative retinal vascular growth there occur quantitative changes in the ESAF normally present in the retina and vitreous humour, rather than de novo synthesis or release of a disease-specific angiogenic molecule from the retina.

The absence of intravitreal neovascularisation in the normal eye may be ascribed to endogenous inhibitors of angiogenesis,[11,12] which are present in sufficient quantities to inhibit any neovascularisation induced by endogenous angiogenic molecules. One of these vitreal inhibitors has been shown to inhibit collagenase and hence acts in a manner opposing the procollagenase activating action of ESAF.[12] In pathological conditions, however, sufficient angiogenic molecules may diffuse from the retina to overcome the natural avascularity of the tissue.

In an earlier report[10] we showed that destruction of the vasculature of the retina, such as to render it hypoxic, gives rise to elevated levels of ESAF within the retina. We now present evidence that this factor is diffusible and passes into the vitreous, where it is the presumed stimulus to the subsequent preretinal angiogenesis.

Materials and methods

Newborn kittens were incubated for a period of three days in an atmosphere containing 70–80% oxygen. They were then removed abruptly to normal room air for a period of between nine and 18 days before administration of an excess of pentobarbital and vitrectomy under deep anaesthesia. Normal healthy kittens not exposed to hyperoxia were used as controls.

Vitreous humour from each individual kitten was homogenised for 15 seconds at 4°C in an equal volume of 50 mM NH_4 HCO_3 buffer (pH 7·9) containing 2 M $MgCl_2$ and was clarified by centrifugation at 20000 *g* (1 h, 4°C). The supernatant was assayed for protein[13] prior to ultrafiltration on a YM5 filter membrane (5000 Mr exclusion limit) (Amicon Ltd, Stonehouse, Gloucs) with five volumes of bicarbonate buffer.

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*Taylor CM, Weiss JB. Quantitation of ESAF in a range of mammalian tissue. In preparation.

†Elstow SF, Kissun RD, Schor AM, McLeod, Weiss JB, Garner A. A low molecular mass angiogenic fraction in vitreous from patients with extraretinal neovascularisation. In preparation.

Correspondence to Dr C M Taylor.

The ultrafiltrate was reduced by rotary evaporation to a volume of 5 ml and applied to an octodecyl silica column (Analytichem, Harbor City, California). Bound low molecular weight angiogenic material was eluted with methanol.

Assay of angiogenic material for its ability to activate procollagenase was performed according to the method of Weiss *et al.*[9] Results were expressed as μg collagen degraded/h/mg protein in the supernatant.

Results

Extracts of vitreous humour from both control and oxygen treated kittens contained significant quantities of a low molecular mass angiogenic factor. Reverse phase chromatography permitted the isolation of a purified fraction which when applied to a P2 column eluted in a position consistent with ESAF.[8] This fraction was assayed for its ability to activate procollagenase. From the results (Table 1) it is apparent that vitreous humour from oxygen treated kittens contains significantly increased quantities of low molecular weight procollagenase activating material as compared to controls.

Table 1 *Activation of procollagenase* by ESAF† present in the vitreous humour of control and oxygen treated kittens*

Experiment	μg Collagen degraded/h/mg protein in supernatant	
	Oxygen treated	Control
1	2·00	0·50
2	1·26	1·11
3	0·51	0·26
4	1·00	0·59
5	2·25	0·47
6	1·61	0·09
7	1·04	
8	0·91	
9	0·67	
Mean	1.25	0·50
SD	0·59	0·35
p=0·01		
Mean retinal results from Taylor *et al.*[10]	2·24	0·59

Paired vitreous humours from individual kittens were used in each experiment.

*The procollagenase used in the assay had very little intrinsic collagenolytic activity; enzyme without ESAF degraded less than 0·35 μg collagen per hour.

†ESAF itself in the absence of procollagenase had no effect on the collagen substrate.

SD=standard deviation.

Variation within the two groups is likely to reflect individual differences between animals, though a temporal relationship between duration of exposure to a normal atmosphere and the quantities of ESAF present may exist in the oxygen treated group.

These results complement our earlier study of the effects of hypoxia on the angiogenic potential of the developing kitten retina.[10] The differences between the vitreous humour samples from the oxygen treated and control kittens were smaller than those found in the retinal extracts.

Although the quantities of ESAF in the control vitreous humour and retinae (expressed as μg collagen degraded/h/mg protein) were similar, in the oxygen treated kittens the retinae contained approximately twice as much ESAF as comparable samples of vitreous humour. Hence an imbalance existed between the quantities of ESAF present in the retinae and vitreous humours of oxygen treated kittens.

Discussion

The concept of tissue hypoxia as a stimulus to angiogenesis is not new,[14-17] and a hypoxic gradient has been shown to be mandatory for wound healing angiogenesis.[18]

There is also evidence that a similar situation pertains in respect of the retina, but it was largely circumstantial until we demonstrated that artificially induced retinal ischaemia is followed by raised tissue levels of a specific angiogenic fraction (ESAF).[10] This provides an explanation for the revascularisation of the retina which occurs in newborn kittens subjected to vaso-obliterative doses of oxygen. However, such animals also develop preretinal new vessels, and our findings in the present report support the view that this reflects diffusion of the initially intraretinal factor into the vitreous. It appears, moreover, that the promotion of new vessel growth is a function of opposing influences, since there is, even in control animals, a basal level of ESAF (0·50 μg collagen degraded/h/mg protein). The presence of antiangiogenic substance(s) in the vitreous of other species is well established.[11,12,19] The level of ESAF in the vitreous compares with that found in the retina of the same animals (0·59 μg collagen degraded/h/mg protein), which suggests that there is little obstacle to passage of the factor across the inner limiting membrane of the retina. It may, in passing, be noted that the presence of significant quantities of ESAF in the retina is likely to be a reflection of the normal processes of developmental vascularisation occurring in the neonate kitten at birth. When the level of

ESAF rises in the retina in response to ischaemia, this creates a diffusion gradient and an increase in vitreal ESAF concentration which may be sufficient to overwhelm the opposing angiogenic inhibitory substances and permit extraretinal neovascularisation.

The sequence of reduced intraretinal circulation, tissue hypoxia, release of ESAF with diffusion into the vitreous, and subsequent preretinal angiogenesis is not confined to the artificially induced situation in kittens but is likely to be relevant in the context of naturally occurring proliferative retinopathy in man. The presence of angiogenic factor in the vitreous has already been observed in respect of diabetic retinopathy[20 21] and certain other non-diabetic conditions associated with preretinal angiogenesis (Elstow SF, *et al.* in preparation), and its origin from an inadequately perfused retina is entirely consistent with angiographic findings.

References

1 Michaelson IC. The mode of development of the vascular system of the retina, with some observations on its significance for certain retinal diseases. *Trans Ophthalmol Soc UK* 1948; **68:** 137–80.

2 Ashton N. Retinal vascularization in health and disease. *Am J Ophthalmol* 1957; **44:** 7–17.

3 Ashton N, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. *Br J Ophthalmol* 1954; **38:** 397–432.

4 Wise GN. Retinal neovascularization. *Trans Am Ophthalmol Soc* 1956; **54:** 729–826.

5 Smith R. Thrombotic glaucoma: a clinico-pathological study. *Proc Int XVII Congr Ophthalmol 1954.* Montreal, New York: 1955, **2:** 1164–75.

6 Kissun RD, Garner A. Vasoformative properties of normal and hypoxic retinal tissue. *Br J Ophthalmol* 1977; **61:** 394–8.

7 Kissun RD, Hill CR, Garner A, Phillips P, Kumar S, Weiss JB. A low molecular weight angiogenic factor in cat retina. *Br J Ophthalmol* 1982; **66:** 165–9.

8 Elstow SF, Schor AM, Weiss JB. Bovine retinal angiogenesis factor is a small molecule. *Invest Ophthalmol Vis Sci* 1985; **26:** 74–9.

9 Weiss JB, Hill CR, Davis RJ, McLaughlin B, Sedowofia KA, Brown RA. Activation of procollagenase by low molecular weight angiogenesis factor. *Biosci Rep* 1983; **3:** 171–7.

10 Taylor CM, Weiss JB, Kissun RD, Garner A. Effect of oxygen tension on the quantities of procollagenase-activating angiogenic factor present in the developing kitten retina. *Br J Ophthalmol* 1986; **70:** 162–5.

11 Raymond L, Jacobson B. Isolation and identification of stimulatory and inhibitory growth factors in vitreous. *Exp Eye Res* 1982; **34:** 261–8.

12 Taylor CM, Weiss JB. Partial purification of a 5·7 K glycoprotein from bovine vitreous which inhibits angiogenesis and collagenase activity. *Biochem Biophys Res Commun* 1985; **133:** 911–6.

13 Lowry OH, Rosenbrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem* 1951; **193:** 265–75.

14 Brem S, Cotran R, Folkman J. Tumor angiogenesis: a quantitative method for histological grading. *J Natl Cancer Inst* 1972; **48:** 347–56.

15 Folkman J. Tumor angiogenesis. *Adv Cancer Res* 1974; **10:** 331–58.

16 Goodson WH, Andrews WS, Thakral KK, Hunt TK. Wound oxygen tension of large versus small wounds in man. *Surg Forum* 1979; **30:** 92–5.

17 Gospodarowicz D, Thakral KK. Production of a corpus luteum angiogenic factor responsible for proliferation of capillaries and neovascularisation of the corpus luteum. *Proc Natl Acad Sci USA* 1977; **75:** 847–51.

18 Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis—effect of oxygen gradients and inspired oxygen concentration. *Surgery* 1981; **90:** 262–70.

19 Jacobson B, Dorfman T, Basu PK, Hasany SM. Inhibition of vascular endothelial cell growth and trypsin by vitreous. *Exp Eye Res* 1985; **41:** 581–95.

20 Glaser BM, D'Amore PA, Michels RG. The effect of human intraocular fluid on vascular endothelial cell migration. *Ophthalmology* 1981; **88:** 986–91.

21 Hill CR, Kissun RD, Weiss JB, Garner A. Angiogenic factor in vitreous from diabetic retinopathy. *Experientia* 1983; **39:** 583–5.

Accepted for publication 27 November 1986.

British Journal of Ophthalmology, 1988, 72, 5–10

Clinical and immunopathological studies of pars planitis in a family

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SUMMARY We examined a family in which two brothers with identical HLA typing have pars planitis with snowbanking. Immunopathological studies of one of their eyes showed that in the area of snowbanking over the pars plana there was mild to moderate inflammatory cell infiltration, consisting of mostly Pan T (Leu 4+) lymphocytes. The ratio of T helper/inducer to T suppressor/cytotoxic cells was approximately 10:1. Few macrophages (OKM1+) were identified. Very few B cells and no NK cells were observed. Some retinal vessels had a perivascular infiltration consisting of mostly T lymphocytes. Most of the inflammatory cells bore class II antigens (HLA-DR+), while T cells bore few IL-2 receptors (anti-TAC+). The snowbank consisted mainly of glial elements (GFAP+) and basement membrane components (type IV collagen and laminin) with the predominant cell the Müller cell (Mü+). A site of inflammation at the iris-ciliary body junction also stained for B cells (Leu 14+). These findings suggest that the snowbank could be formed by the glial elements of the peripheral retina. The chronic inflammation in pars planitis appears to consist of helper T cells, both in the pars plana, and the retinal vasculature.

Pars planitis is an inflammation of the ciliary body, vitreous base, and peripheral retina.[1] First called peripheral uveitis,[1 2] it has also been called chronic cyclitis[3] in addition to pars planitis.[4] Clinically pars planitis is characterised by the formation of snowbanking, which is seen as a massive exudation over the ora serrata. Macular oedema and cataracts often decrease vision. Less commonly, retinal detachments, neovascularisation, and intraocular haemorrhage occur. The anterior segment of the eye usually remains quiet. Children and young adults are most often affected. Treatment may include cryotherapy,[5] depot steroid injection,[6] systemic immunosuppression with steroids and cytotoxic agents,[7] and systemic treatment with cyclosporine A.[8] It must be distinguished from sarcoid uveitis and *Toxocara canis* infection.

Previous histopathological studies of pars planitis have shown evidence of a retinal vasculitis, cyclitis,[9] and choroiditis.[3 10] Fibroglial proliferation in the area of the snowbank has been described.[11] The mechanisms that lead to the production of the snowbanks are not known.

Although generally not thought to be familial, there have been reports of siblings having the disease.[3 12 13] No genetic linkage to HLA loci or other genetic markers have been established, however.

This paper discusses our immunohistochemical study of an eye from a patient with pars planitis. The brother, who also has pars planitis, the patient, and their mother were HLA typed.

Case report

The patient was a 16-year-old white male with a three-year history of pars planitis in both eyes. The left eye had been more involved than the right. In that eye he had developed band keratopathy, vitreous reaction, snowbanking, traction retinal detachments, and vitreous haemorrhages. He underwent lensectomy, vitrectomy, and retinal detachment repair in the left eye. The patient had recurrent hyphaemas, vitreous haemorrhage, and rubeosis in

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that eye, leading to no light perception and pain. The eye was enucleated eight months postoperatively.

The patient was started on cyclosporine A for his remaining eye at a dose of 9·5 mg/kg/day. Vision before treatment was 20/100 and after three months of treatment was 20/63, with improvement in his chronic inflammation.

The patient's brother also had bilateral pars planitis with snowbanking. The mother's eyes were normal. Although the father was not available for HLA typing, the patient, his brother, and their mother were typed, with the following results: patient, A2, A3; B7, B57; DR2, DR7; brother, A2, A3; B7, B57; DR2, DR7; mother, A2, A32; B7, B27; Cw2; DR2, DR7.

The patient's lymphocytes were tested, and did not respond to S-antigen. In addition, he had a normal peripheral T-cell count.

CONTROL EYE

A second eye without pars planitis was studied as a control. The patient was 37 years old and had a blind painful eye. There had been a knife injury at age 2. At age 26 the patient had a corneal graft. There was a retinal detachment one year later that was repaired. The detachment repair failed. Prior to enucleation there were band keratopathy and glaucoma.

Materials and methods

The enucleated eyes were snap frozen and embedded in optimal cutting temperature compound (OCT). Frozen 4 μm sections were prepared and stored at − 4°C for 48 hours prior to staining. Mouse-antihuman monoclonal antibodies from Becton Dickinson (Sunnyvale, CA) were used to identify various lymphocyte subpopulations and other antigenic determinants. Monoclonal antibodies detecting determinants on bone marrow monocytes were OKM1. Antibodies specific for T cells were Leu 2a, Leu 3a, Leu 4, Leu 8 and Leu 15. Leu 7 was specific for natural killer (NK) cells. Leu 14 was specific for B-cells. In addition antibodies against the major histocompatibility IL-2 complex (MHC) class II antigen (HLA-DR), the Il 2 receptor (anti-TAC), retinal S antigen (anti-S), Müller cell components (Mü), and glial fibrillary acid protein (GFAP) were used. Immunohistochemistry studies were performed by the avidin-biotin-peroxidase (ABC) method.[14] The sections were fixed in acetone for 5 minutes, transferred to Tris-buffered saline, 0·05 M, at a pH of 7·6, and then immersed in 10% normal horse serum in buffer for 5 minutes. The primary monoclonal antibodies were used at a concentration of 1 to 2 μg/ml. After incubation in a moist chamber at room temperature for one hour the slides were washed in Tris-buffered saline, then the secondary antibody, biotin-conjugated horse antimouse IgG, 1:200, was layered on the slides. The slides were again incubated in a moist chamber at room temperature for another hour. After washing in Tris-buffered saline, ABC 1:100 was applied for 45 minutes. The slides were washed again in Tris-buffered saline, and incubated in diaminobenzide-8% nickel sulphate and 3% H_2O_2 solution. The slides were counterstained with methyl green (1% in methanol), dehydrated, and cleared as in routine processing.

Immunofluorescence staining was also performed. Air dried frozen sections were washed twice in phosphate buffered saline (PBS) (pH 7·4). The slides were incubated for 30 minutes at room temperature in a moist chamber with the primary antibodies (against collagen type I, collagen type III, collagen type IV, and laminin). They were then washed three times in PBS. Then the slides were incubated with fluorescein labelled antibody against the primary antibody IgG for 30 minutes in a moist chamber at room temperature. The slides were then washed three times in PBS, mounted with Gelvatol, and covered with glass coverslips.

Results

Macroscopic. The globe measured 22×20×23 mm. A 360° scleral buckle was present at the anterior sclera. The cornea was opaque. The anterior chamber was not visible. The eye was transluscent. The globe was opened horizontally. A total funnel-shaped retinal detachment was seen.

Microscopic. The corneal stroma was compressed. Descemet's membrane was intact. The corneal endothelium was markedly attenuated. The anterior chamber was shallow and filled with blood. The angle structure was completely closed by synechiae. A few chronic inflammatory cells (plasma cells and lymphocytes) could be seen at the angle. The anterior iris tissue was covered partially by Descemet's membrane and a thin layer of fibrovascular tissue. Scattered chronic inflammatory cells were seen in the iris stroma. The ciliary body showed mild oedema, atrophy, and chronic inflammatory cell infiltration. The lens was absent. A thick layer of fibrous-like tissue (snowbanking) was present at the base of the ciliary body and pars plana (Fig. 1A). The pars plana showed moderate to marked oedematous change. There was mild to moderate lymphocytic cell infiltration in the pars plana region. The retina was totally detached in a funnel-shaped configuration. Its structure was completely disorganised and showed gliosis. There was one area of iron staining in the retina, and in another area there were a few epithelial cells which may represent lens epithelial cells or retinal

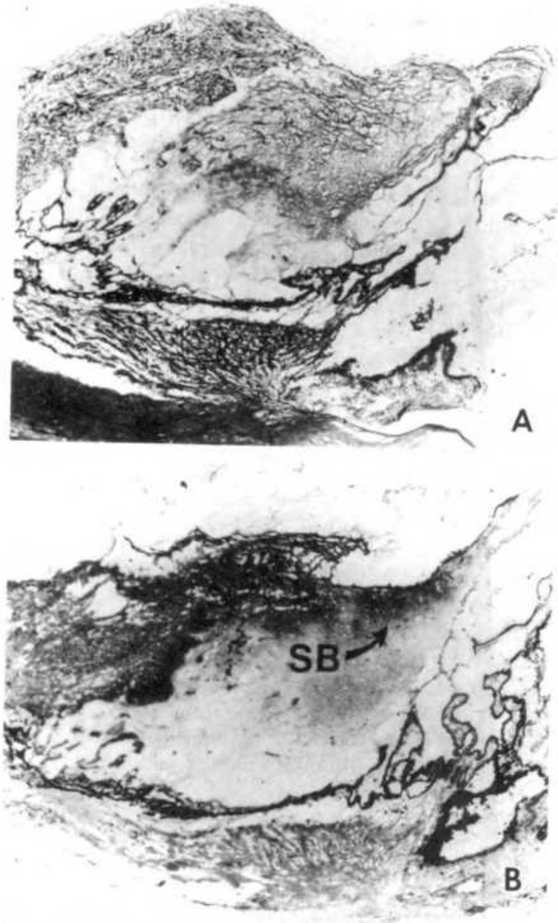


Fig. 1A: *The snowbanking was continuous with an area of disorganised glial tissue continuous with the retina (haematoxylin and eosin).* B: *The area of snowbanking over the pars plana stained heavily for GFAP (arrow), confirming the presence of glial elements.*

pigment epithelium (RPE) metaplasia. The vitreous cavity was compressed by the detached retina and contained a small amount of old blood. A small amount of proteinacious material was seen in the subretinal space. The RPE showed mild to moderate irregularity with focal hyperplasia and hypertrophic changes, more peripherally. The choroid was relatively intact except at the peripheral region, where a scattered lymphocytic infiltration was identified. A large scleral buckle was seen near the pars plana region on one side and peripheral retina on the other side. Very mild chronic inflammation was seen around the buckle. The posterior sclera was mildly thickened. The optic nerve was atrophic with loss of neural substance and gliotic changes.

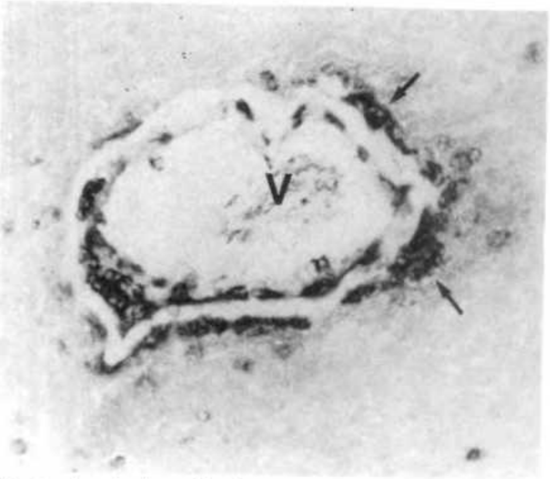


Fig. 2 *A retinal vessel had a perivascular Leu 4 positive T cell infiltrate (arrows).*

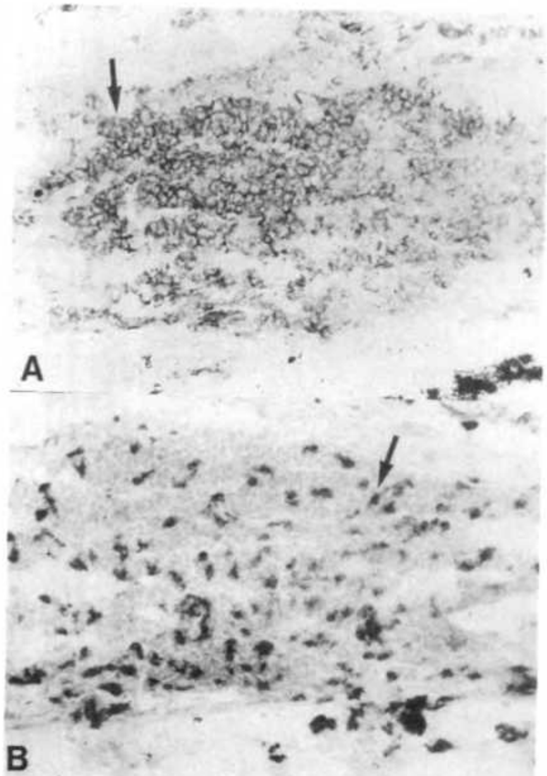


Fig. 3 *The T cell infiltrate beneath the pars plana was predominantly Leu 8 positive T helper cell (arrow, panel A) as opposed to Leu 2 positive suppressor/cytotoxic cell (arrow, panel B).*

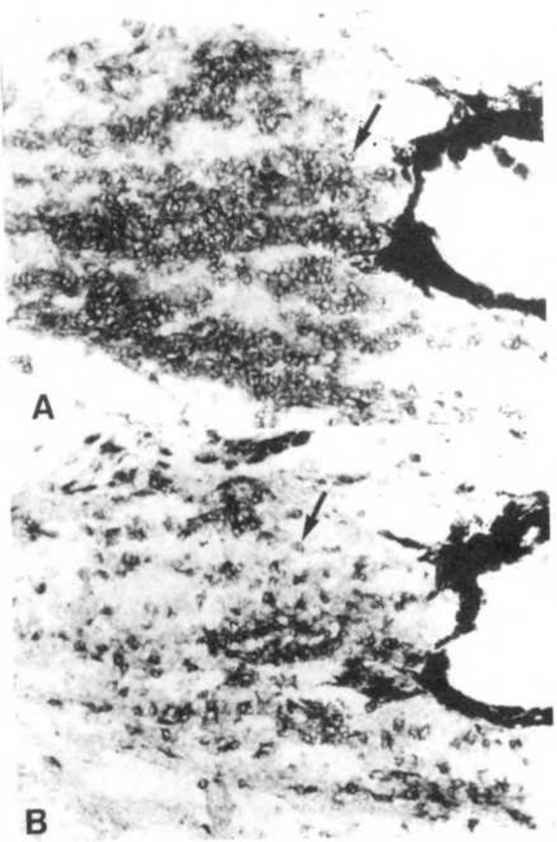


Fig. 4 *An area at the junction of the iris and ciliary body stained heavily for Leu 14 B cells (arrow, panel A) and less heavily for Leu 4 T cells (arrow, panel B).*

The immunopathological studies showed that the large area of snowbanking over the pars plana was continuous with disorganised retinal glial tissue. The snowbank stained heavily with antibody directed against glial fibrillary acid protein, confirming the presence of glial elements (Fig. 1B). Staining with Mü for Müller cells was also positive. There was, however, no staining for retinal S antigen.

Within the snowbank a mild inflammatory infiltrate of Leu 4 positive T cells was present. A retinal perivascular Leu 4 positive T cell infiltration was also seen (Fig. 2). The helper to suppressor ratio of cells was not able to be determined because of the small numbers of inflammatory cells in the peri-vascular region. A Leu 4 positive T cell infiltrate was also seen within the pars plana itself. The T cell infiltrate within the pars plana was predominantly Leu $3a^+/8^+$ T helper cell, as opposed to Leu 2a T suppressor cell (Fig. 3). Staining in the pars plana area was largely negative for Leu 7 NK cells, Leu 14 B cells, and OKM1 monocytes/macrophages. Most of the inflammatory cells bore class II, DR antigens, while the anti-TAC antibody directed against IL-2 receptors did not stain cells in most areas.

Cells at the iris root stained heavily for Leu 14 B cells and less heavily for Leu 4 positive T cells (Fig. 4). More Leu 3a helper cells than Leu 2a suppressor cells were observed.

Immunofluorescent staining was greater for collagen type IV and laminin than for collagen types I and III (Fig. 5).

Table 1 summarises the immunohistological findings in the patient's eye.

In the control eye the area under the pars plana was

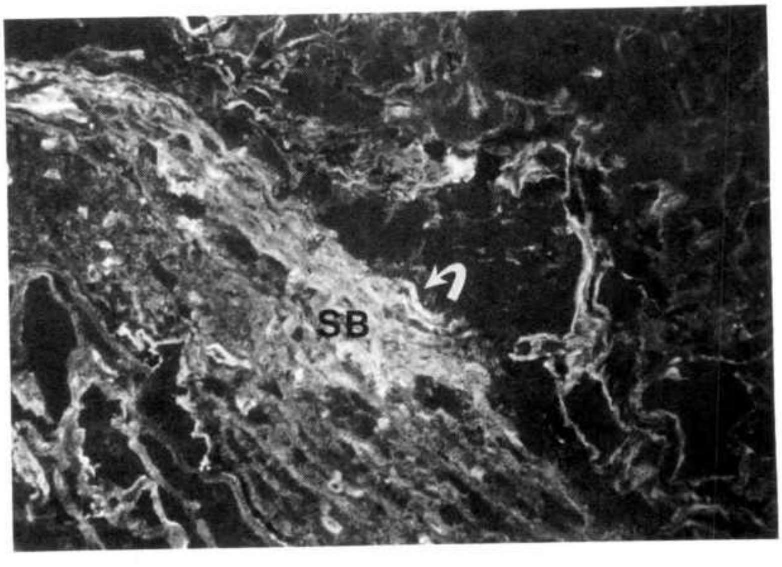


Fig. 5 *The snowbank stained positively with immunofluorescence for collagen type IV (arrow).*

Table 1 *Immunohistologic findings in pars planitis eye*

Antibody	*Specificity*	*Snowbank*	*Pars plana*	*Iris/ciliary body*
Leu 2	Suppressor/cytotoxic T cells[15]	ND	+	+
Leu 3	Helper T cells[15]	ND	+++	++
Leu 4	Pan T cell[16]	++	++++	++
Leu 7	Natural killer cells[17]	–	–	–
Leu 8	Helper T cells[15]	ND	+++	ND
Leu 10	HLA DQ[18]	–	++	–
Leu 14	B cells[19]	–	–	++++
Leu 15	Cytotoxic cells[20]	–	–	–
OKM$_1$	Monocytes/macrophages[21]	–	–	–
Anti-DR	HLA-DR[22]	+++	+++	+++
Anti-TAC	Interleukin 2 receptor[23]	–	–	–
Anti-S-Ag	S antigen[24]	–	–	–
Anti-Mu	Muller cells[25]	++		
Anti-GFAP	Glial fibrillary acid protein[26]	++++		
Anti-coll I	Collagen Type I[27]	–	–	–
Anti-coll III	Collagen Type III[27]	–	–	–
Anti-coll IV	Collagen Type IV[27]	++	–	–
Anti-laminin	Laminin[27]	++	–	–

free of inflammatory cells. There was no retinal vasculitis. No area of snowbanking was present.

Discussion

We report here the immunopathological features of an eye with pars planitis. The observation that snowbanking consists mainly of glial elements[11] is confirmed by staining with anti-Müller cell antibody and GFAP. Müller cells proliferate in response to factors produced by activated lymphocytes,[28] suggesting a means whereby the snowbank formation is stimulated by inflammation. In turn, Müller cells can express class II MHC molecules and present antigen to T cells,[29] contributing to the inflammation themselves. Type IV collagen and laminin were the major collagen glycoproteins in this snowbank. They are formed by glial cells rather than fibroblasts, as are collagen types I and III. This suggests that the snowbank could be formed from the glial elements of the peripheral retina which was observed by electron microscopic studies in the case studied by Kenyon *et al.*[11] Among the various uveitis entities pars planitis appears to be unique in the propensity to stimulate a glial response of this nature, with the exception of the subretinal fibrosis and uveitis syndrome[30] and cyclitic membrane formation.[31] These observations show evidence for a postinflammatory glial proliferation.

Anti-rod-cone (S antigen) antibody does not label the snowbank, suggesting that the photoreceptor cells did not contribute to its formation. This is in spite of the observation that one out of three patients with pars planitis have peripheral lymphocytes that respond to stimulation with S antigen.[32] In this case the patient did not respond with lymphocyte proliferation to S antigen, however.

The T cell predominance in the pars plana shows that the inflammatory response in this case is possibly cell mediated. There were few B cells posterior to the junction of the iris and ciliary body, where the pocket of B cells and T cells was found. There were not enough cells in the vitreous of our specimen to compare with the snowbank cellular makeup. Our patient, like other patients with pars planitis[33] had normal peripheral T cell counts. The high ratio of helper cell to suppressor cell in this eye parallels the finding of lymphoid accumulations in several systemic autoimmune disorders such as rheumatoid arthritis[34] and chronic active hepatitis,[35] suggesting an active T cell mediated process in the eye.

The eye studied represents an end stage state of disease. Any comparison with eyes that have pars planitis at earlier stages must be made with caution. The effects of the chronicity of the pathology and the effects of surgery must be considered. The eye studied had surgery eight months prior to enucleation, which might have led to some inflammation. A control eye with prior retinal detachment surgery was chosen to see if detachment surgery alone could produce this picture of inflammation. The absence of inflammation in the control eye indicates that longstanding retinal detachment after surgery does not always cause inflammation by itself.

There have been earlier reports of familial pars planitis.[3 12 13] In our study the brothers not only each have bilateral pars planitis, but also share the identical HLA antigens, HLA A2, A3; B7, B57; DR2, DR7. In the study by Augsburger *et al.*[13] one of two families had three children with pars planitis sharing HLA A2, A11, B5, B40, and Cw3, while the unaffected siblings had different HLA combinations. In another family they studied there was no such

HLA identity between siblings with disease. More data with larger pedigrees are required to establish the presence of a susceptibility gene or gene combination, as suggested by the one small family reported here. Attempts to study the population frequency of the various HLA antigens in pars planitis in the past have not shown a definite pattern. Ohno *et al.* showed a highly significant association between HLA-B27 and adult onset iridocyclitis, but not between any HLA antigen and chronic cyclitis (pars planitis).[36]

In summary, we report a case of pars planitis with positive family history. The ocular inflammatory process consists of glial elements with predominantly T helper cell infiltrates.

The control eye was provided by Dr Stephen Ginsberg and Dr Garth Stevens. Very helpful secretarial assistance was provided by Ms Elayne Coggins.

References

1 Schepens CL. Examination of the ora serrata region: its clinical significance. *ACTA 16 Concilium Ophthalmologicum Britannia.* London: British Medical Association, 1950; 2: 1384–93.

2 Brockhurst RJ, Schepens CL, Okamura ID. Uveitis II. Peripheral uveitis: clinical description and differential diagnoses. *Am J Ophthalmol* 1960; 49: 1257–66.

3 Kimura SJ, Hogan MJ. Chronic cyclitis. *Trans Am Ophthalmol Soc* 1963; 61: 397–413.

4 Welch RB, Maumenee AE, Wahleu HE. Peripheral posterior segment inflammation, vitreous opacities, and edema of the posterior pole. Pars planitis. *Arch Ophthalmol* 1960; 64: 540–9.

5 Aaberg TM, Cesarz TJ, Flickinger RR. Treatment of pars planitis. I. Cryotherapy. *Surv Ophthalmol* 1977; 22: 120–5.

6 Schlaegel TF, Weber JC. Treatment of pars planitis. II. Corticosteroids. *Surv Ophthalmol* 1977; 22: 120–30.

7 Schlaegel TF. *Ocular toxoplasmosis and pars planitis.* New York: Grune and Stratton, 1978: 334–7.

8 Nussenblatt RB, Palestine AG, Chan C-C. Cyclosporine A therapy in the treatment of intraocular inflammatory disease resistant to systemic corticosteroids and cytotoxic agents. *Am J Ophthalmol* 1983; 96: 275–82.

9 Pederson JE, Kenyon KR, Green WR, Maumenee AE. Pathology of pars planitis. *Am J Ophthalmol* 1978; 86: 762–74.

10 Brockhurst RJ, Schepens CL, Okamura ID. Uveitis. 3 Peripheral uveitis. Pathogenesis, etiology, and treatment. *Am J Ophthalmol* 1961; 51: 19–25.

11 Kenyon KR, Pederson JE, Green WR, Maumenee AE. Fibroglial proliferation in pars planitis. *Trans Ophthalmol Soc UK* 1975; 95: 391–7.

12 Witmer MJ, Korrer G. Uveitis in Kindesalter. *Ophthalmologica* 1966; 152: 277–82.

13 Augsburger JJ, Annesley WHH, Sergott RC, Felberg NT, Bowman JH, Raymond LA. Familial pars planitis. *Ann Ophthalmol* 1981; 13: 553–7.

14 Hsu SM, Raine L, Fauger H. The use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase technique: a comparison between ABC and unlabeled antibody (PAP) procedures. *J Histochem Cytochem* 1981; 29: 577–80.

15 Engleman EG, Benike CJ, Glickman E, Evans RL. Antibodies to membrane structures that distinguish suppressor/cytotoxic and helper T lymphocyte subpopulations block the mixed leukocyte reaction in man. *J Exp Med* 1981; 154: 193–8.

16 Ledbetter JA, Evans RL, Lipinski M, Cunningham Rundles C, Good RA, Henzenberg LA. Evolutional conservation of surface molecules that distinguish T lymphocyte helper/inducer and cytotoxic/suppressor subpopulations in mouse and man. *J Exp Med* 1981; 153: 310–23.

17 Abo T, Balch CM. A differentiation antigen of human NK and K cells identified by a monoclonal antibody (HNK-1). *J Immunol* 1981; 127: 1024–9.

18 Chen YX, Evans RL, Pollack MS, *et al.* Characterization and expression of the HLA-DC antigens defined by anti-Leu-10. *Hum Immunol* 1984; 10: 1221–35.

19 Schwanting R, Stein H, Wang CY. The monoclonal antibodies anti-S-HC1–1 and anti-S-HC1–3 allow the diagnoses of hairy cell leukemia. *Blood* 1985; 65: 974–83.

20 Landay A, Gantland L, Clement LT. Characterization of a phenotypically distinct subpopulation of Leu-2 cells which suppresses T-cell proliferative responses. *J Immunol* 1983; 131: 2757–61.

21 Breard J, Reinherz EL, Kung PC, *et al.* A monoclonal antibody reactive with human peripheral blood monocytes. *J Immunol* 1980; 124: 1943–8.

22 Reinherz EL, Kung PC, Pesahdo JM, *et al.* 1a determinants on human T cell subsets defined by monoclonal antibody: activation stimuli required for expression. *J Exp Med* 1979; 150: 1472–82.

23 Uchiyama T, Broder S, Waldman TA. A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human t-cells. I. Production of anti-Tac monoclonal antibody and distribution of Tac(+) cells. *J Immunol* 1981; 126: 1393–7.

24 Mirshahi M, Faure JP, Brisson P, Falcon J, Geurlotte J, Collin JP. S-antigen immunoreactivity in retinal rods and cones and pineal photosensitive cells. *Biol Cell* 1984; 52: 195–8.

25 Chan C-C, Rozenszajn LA, Nussenblatt RB, *et al.* Monoclonal antibodies to Müller's cells of the retina. *Invest Ophthalmol Vis Sci* 1984; 25: 1007–12.

26 Eng LF, DeArmond SJ. Immunohistochemistry of the glial fibrillary acidic protein. In: Zimmerman HM, ed. *Progress in neuropathology.* New York: Raven Press 1983: 19–39.

27 Martin GR, Timpl R, Muller PK, Kuhn K. The genetically distinct collagens. *Trends in Biochemical Sciences* 1985; 10: 285–7.

28 Roberge FG, Caspi RR, Chan C-C, Kuwabara T, Nussenblatt RB. Long term culture of Muller cells from adult rats in the presence of activated lymphocytes/monocytes products. *Curr Eye Res* 1985; 4: 975–82.

29 Roberge FG, Caspi RR, Chan C-C, Nussenblatt RB. Antigen presentation by retinal glial cells. *4th International symposium on the immunology and immunopathology of the Eye.* Italy, 1986 (in press).

30 Palestine AG, Nussenblatt RB, Chan C-C, Hooks JJ, Friedman L, Kuwabara T. Histopathology of the subretinal fibrosis and uveitis syndrome. *Ophthalmology* 1985; 92: 836–44.

31 Chan C-C, Fujikawa LS, Rodrigues MM, Stevens G, Nussenblatt RB. Immunohistochemistry and electron microscopy of cyclitic membrane. A case report. *Arch Ophthalmol* 1986; 104: 1040–5.

32 Nussenblatt RB, Gery I, Ballantine EJ. Cellular responsiveness of uveitis patients to retinal S-antigen. *Am J Ophthalmol* 1980; 89: 173–9.

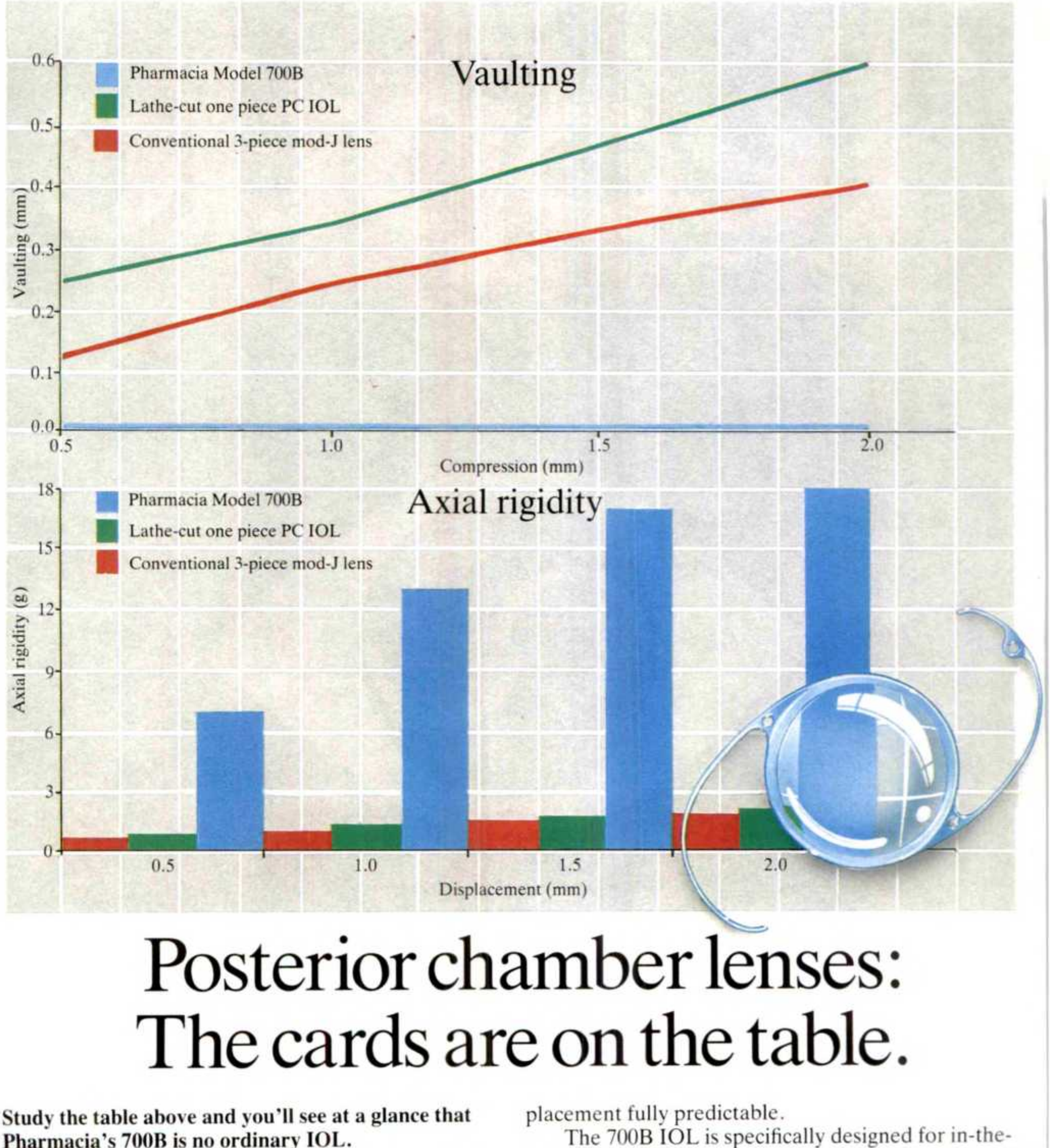
33 Yokoyama MM, Matsui Y, Yamashiroya HM, *et al.* Humoral and cellular immunity studies in patients with Vogt-Koyanagi-Harada syndrome and pars planitis. *Invest Ophthalmol Vis Sci* 1981; 20: 364–70.

34 Janossy G, Duke O, Poulter LW, *et al.* Rheumatoid arthritis: a disease of T-lymphocyte/macrophage immunoregulation. *Lancet* 1981; ii: 839–42.

35 Si L, Whiteside TL, Schade RR, Van Thiel DH. Studies of lymphocyte subpopulations in the liver tissue and blood of patients with chronic active hepatitis (CAH). *J Clin Immunol* 1983; 3: 408–19.

36 Ohno S, Kimura SJ, O'Connor RG, Char DH. HLA antigens and uveitis. *Br J Ophthalmol* 1977; 61: 62–4.

Accepted for publication 4 December 1986.



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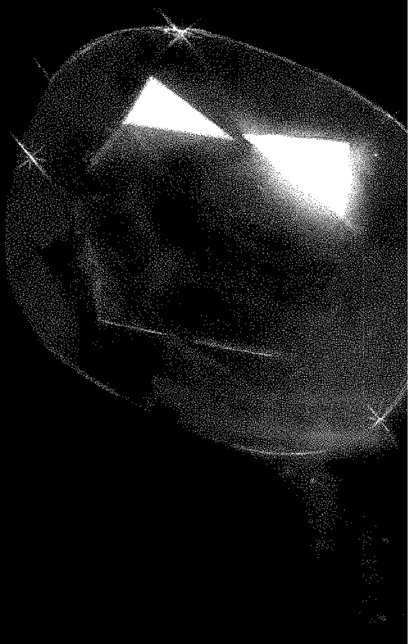

British Journal of Ophthalmology, 1988, 72, 11–16

Anterior segment ischaemia following laser photocoagulation in a patient with systemic lupus erythematosus

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SUMMARY The authors report the occurrence of occlusive retinal arterial disease and retinal neovascularisation in a 44-year-old woman with systemic lupus erythematosus (SLE). Two days after uncomplicated panretinal photocoagulation the patient developed an acute anterior segment ischaemic syndrome. To our knowledge this complication has not been reported in any other patient following laser photocoagulation or in association with SLE.

Systemic lupus erythematosus (SLE) is a systemic disease of unknown aetiology in which the basic pathogenic mechanism is deposition of immune complexes, activation of complement, and resulting inflammation.[1] The ocular manifestations of SLE include involvement of the lids, cornea, retina, and optic nerve. Retinal haemorrhages and cotton-wool spots are the most common manifestations of retinal involvement.[2] Patients have been reported to develop occlusive retinal arterial disease,[3-11] with retinal neovascularisation occurring in some cases.[3-6]

Anterior segment ischaemia is manifest by pain, reduced vision, corneal oedema with striate keratopathy, and acute iridocyclitis. Posterior synechiae, peripheral anterior synechiae, iris atrophy, cataract, and even phthisis bulbi can develop after an episode of anterior segment ischaemia. This complication has been reported following various operative procedures such as muscle surgery,[12-16] retinal detachment surgery, [17-21] cyclocryotherapy,[22 23] and extracapsular cataract extraction with posterior chamber intraocular lens implantation.[24] It has also been described in association with systemic diseases including occlusive cerebrovascular disease[25] and chronic myelogenous leukaemia.[26] Patients with sickle cell haemoglobinopathy are at particular risk of developing anterior segment ischaemia following retinal detachment surgery.[27 28]

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In this report we describe the development of acute anterior segment ischaemia following panretinal photocoagulation for retinal neovascularisation in a patient with SLE. To our knowledge this syndrome has not been reported following panretinal photocoagulation or in association with SLE or laser photocoagulation in any other patient.*

Case report

A 44-year-old white woman presented to the Retinal Vascular Center of the Wilmer Ophthalmological Institute with a two-week history of blurred vision in the right eye. A diagnosis of SLE had been made at the National Institute of Health six years previously, and the patient had been on varying doses of prednisone since that time. Her past medical history was significant, with deep-vein thrombophlebitis and a pulmonary embolus six years prior to her presentation at Wilmer, and two mild strokes: the first stroke two years previously, associated with right hemiparesis; and the second just four months previously, involving mild paresis of the right arm. The patient was taking 15 mg of prednisone daily at the time of her examination.

The best corrected visual acuity was 10/200 in the

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*This patient has been reported as part of a large series of patients with SLE. (Jabs DA, Fine SL, Hochberg MC, *et al*. Severe retinal vaso-occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol* 1986; 104: 558–63.)

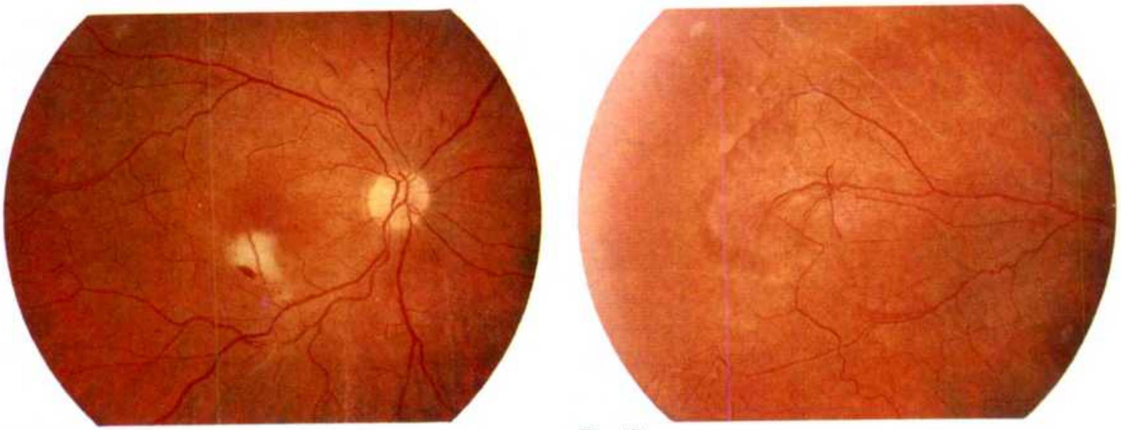

Fig. 1A

Fig. 1B

Fig. 1A *Right fundus revealing mild disc pallor, marked arteriolar attenuation, periarteriolar sheathing, and a cotton-wool spot inferior to the fovea. Retinal neovascularisation extends from the vein superotemporal to the fovea.* B: *View of temporal right fundus showing marked arteriolar compromise with neovascularisation at the margin of perfused and non-perfused retina.*

right eye and 20/20 in the left eye. The pupillary, external, and extraocular motility examinations were all normal. Slit-lamp examination revealed mild ciliary injection for 360° in each eye. There was no cellular reaction or flare in the anterior chamber, no iris neovascularisation was detected, and no lens opacity was seen. The intraocular pressure was 8 mmHg in the right eye and 10 mmHg in the left eye. Ophthalmoscopy of the right eye revealed mild optic disc pallor with marked attenuation of the retinal arterioles and periarteriolar sheathing (Figs. 1A, B). There were several areas of intraretinal haemorrhage and cotton-wool exudation. There were multiple patches of neovascularisation and non-perfused retina with marked arteriolar attenuation in the mid periphery. The left eye also showed arteriolar narrowing with periarteriolar sheathing, intraretinal haemorrhage, and focal non-perfusion (Fig. 2). No discrete areas of neovascularisation were identified in the left eye. Fluorescein angiography confirmed the presence of significant areas of retinal non-perfusion with associated retinal neovascularisation (Fig. 3).

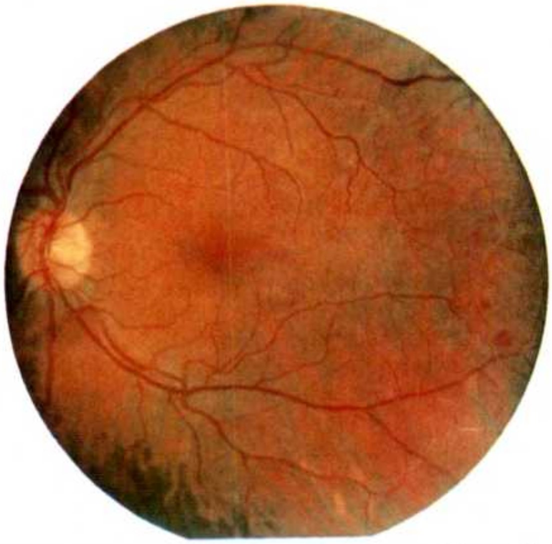

Fig. 2 *There is active retinopathy present in the left eye with haemorrhage and arteriolar sheathing. The retinopathy is less pronounced than in the right eye.*

The patient underwent peripheral scatter argon photocoagulation in the right eye. Only topical anaesthesia was used, and she received 1011 500 µm

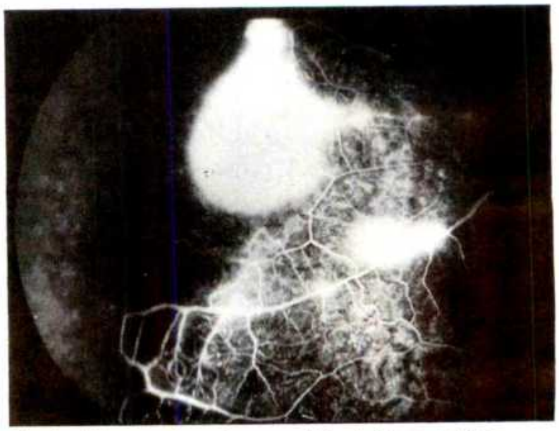

Fig. 3 *Fluorescein angiogram of the right eye. Active neovascularisation is present at the margin of perfused and non-perfused retina.*

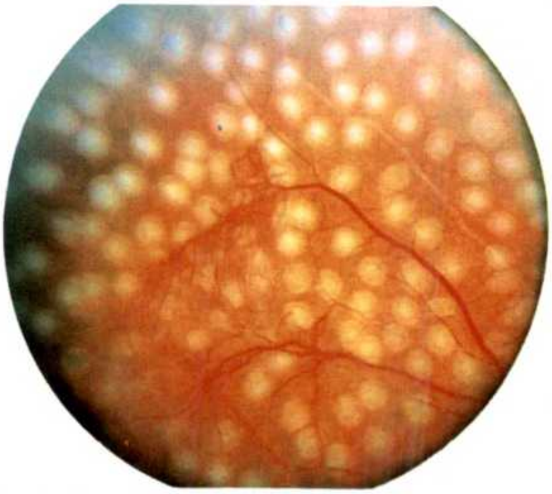

Fig. 4 *Immediate post-laser appearance of the right eye.*

spot size applications of 0·1 second duration varying in power from 250 to 400 milliwatts (Fig. 4). A Goldmann three-mirror contact lens was used and the procedure was completed within 30 minutes.

Two days after this treatment the patient presented with an acutely inflamed, tender right eye (Fig. 5). Her visual acuity was counting fingers. The eye had 4+ conjunctival injection and moderate chemosis, with marked corneal oedema and striae. The anterior chamber was deep, with 4+ suspended red blood cells, which were layering in the filtration angle and on the corneal endothelium. The aetiology of the anterior chamber haemorrhage was unknown, though the authors suspect that perhaps a few undetected twigs of iris neovascularisation or pre-existing dilated iris vessels may have ruptured and caused the haemorrhage. There was also a marked fibrinoid response with early formation of posterior synechiae. Ocular tension by applanation was 2 mmHg in the right eye, compared with 15 mmHg in the left. Acute anterior segment ischaemia was diagnosed and topical prednisolone acetate 1% every four hours and atropine sulphate 1% twice daily were prescribed. The patient was admitted to the Rheumatic Disease Unit for examination and treatment of her active SLE. Her systemic involvement

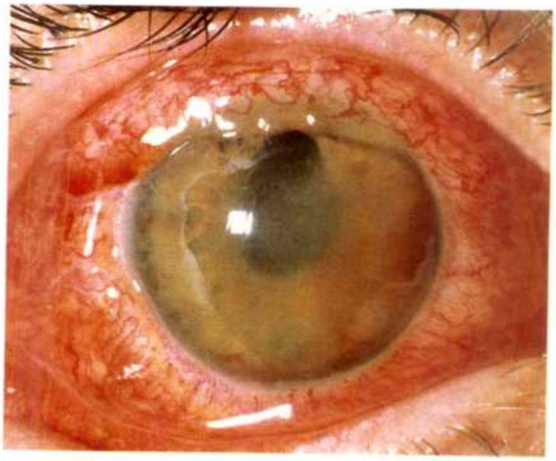

Fig. 5 *Appearance of the right eye two days after argon laser photocoagulation. There is a pronounced conjunctival reaction with corneal oedema and suspended red blood cells in the anterior chamber. Early posterior synechiae formation and a marked fibrinoid response are also present.*

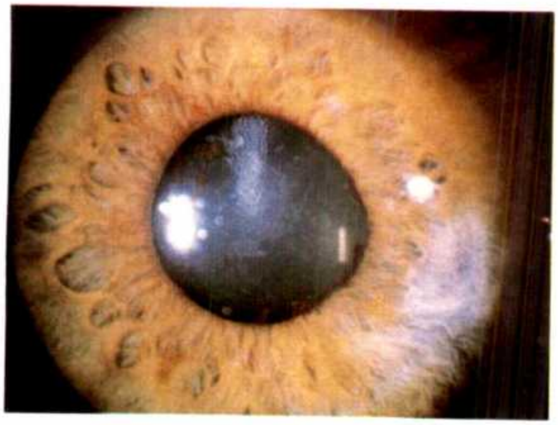

Fig. 6A

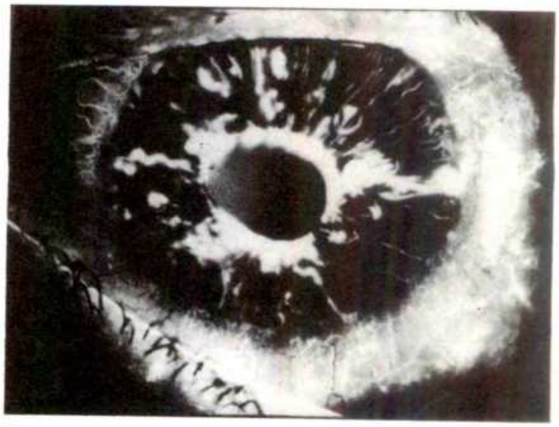

Fig. 6B

Fig. 6A *Ten-week post-treatment appearance of the right eye. Fine iris neovascularisation can be seen as well as pigment clumping on the anterior lens capsule and posterior synechiae. There is a sector of iris atrophy from the 3 o'clock to 5 o'clock position.* B: *Iris angiography confirms the presence of rubeosis.*

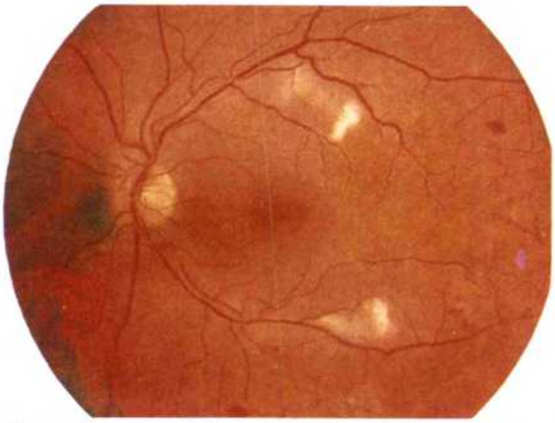

Fig. 7 *Progression of the retinopathy in the left eye over a 10-week period (compare with Fig. 2). There is further arteriolar narrowing and sheathing with cotton-wool exudates.*

was controlled with 80 mg prednisone per day and a three-month course of azathioprine.

On follow-up examination 10 weeks after treatment the patient had visual acuity of 5/200 in the right eye and 20/20 in the left eye. The cornea and anterior chamber were clear. Sector iris atrophy, supporting the diagnosis of anterior segment ischaemia, was present from 3 to 5 o'clock (Fig. 6). Mild rubeosis was noted at the pupillary margin, with posterior synechiae, diffuse angle neovascularisation, and early formation of peripheral anterior synechiae (Figs. 6A, B). Ophthalmoscopy revealed involution of the retinal neovascularisation in the right eye. Examination of the left eye showed progression of retinopathy, with further arteriolar attenuation and increased cotton-wool exudation (Fig. 7).

Discussion

The frequency with which ocular findings are seen in association with SLE is highly variable and depends on the activity of the systemic disease. The early literature reported retinal haemorrhage and cotton-wool spots in 10 to 28% of patients.[29–33] However, Gold *et al.*[2] examined 61 outpatients with SLE and found no retinal haemorrhages and only two (3·3%) patients with cotton-wool exudates. This lower incidence of retinal findings was attributed to better systemic control of the disease. It is believed that the retinopathy of SLE is seen more frequently in acutely ill patients.[2 34] Our patient had heightened systemic activity of her SLE in association with her active retinopathy.

A less common and more serious ocular manifestation of SLE is occlusive retinal arterial disease.[3–11] The precise aetology of the retinal arterial occlusions is obscure. Histopathological study of the central nervous system (CNS) in patients with SLE has revealed numerous microinfarcts secondary to occlusive disease of small arteries and arterioles.[35] These vessel walls did not have significant inflammatory cell infiltration but had undergone fibrinoid degeneration or hyalinisation with necrosis. Histopathological studies of the retina have demonstrated thrombosed arterioles with thickened intimas but have not shown any evidence of active vasculitis.[7 11 34 36] Local deposition of antigen-antibody complexes, embolism, or in-situ thrombosis may all play a part in the occlusive arterial disease of SLE. Gold *et al.*[3] suggested that the occlusive retinal vascular disease seen in patients with SLE may be associated with CNS lupus. It is noteworthy that our patient had two transient ischaemic attacks while she had active retinal arterial occlusive disease.

Retinal neovascularisation has been seen in association with the retinal arterial occlusive disease of SLE[3–6] Neovascularisation of the iris and anterior chamber angle has also been seen in an SLE patient with active retinal occlusive disease.[3] Vitreous haemorrhage may occur,[5 6] and laser photocoagulation has been successful in causing regression of the neovascularisation and preventing vitreous haemorrhage.[4]

Anterior segment ischaemia is a syndrome of acute ocular pain, reduced vision, corneal oedema with Descemet's folds, marked anterior chamber cells and flare which can lead to iris atrophy, posterior synechiae, peripheral anterior synechiae, cataract, and even phthisis bulbi. This syndrome has been seen following retinal detachment surgery[17–21 27 28] and is believed to be related to circulatory compromise of the long posterior ciliary arteries,[19] detachment of the extraocular muscles, or venous outflow insufficiency secondary to vortex vein compression by an encircling element.[20]

Extraocular muscle surgery has also been associated with anterior segment ischaemia.[12–16] Interruption of the anterior ciliary arteries within the rectus muscles has an aetiological role in these cases. Anterior segment ischaemia may follow cyclocryotherapy.[22 23] It has been suggested that this complication results from further reduction in blood flow to an already relatively ischaemic eye induced by the acute cryogenic vascular injury of cyclocryotherapy.[22] Hyperviscosity[26] and generalised cerebrovascular insufficiency[25] have also been reported to cause anterior segment ischaemia.

Anterior segment ischaemia has not been previously described in association with either retinal photocoagulation or SLE. There is no evidence in this case that the laser photocoagulation caused the anteror segment ischaemia. Furthermore, it would be reasonable to assume that our patient was experiencing an element of anterior segment circulatory compromise prior to the photocoagulation. Widespread arterial and arteriolar occlusions are seen in SLE, and this patient was already showing significant retinal circulatory disturbance.

The patient did not have a retrobulbar anaesthetic or a prolonged operative procedure, two factors that may have affected ocular circulation. However, the brief time in which the Goldmann lens was pressing on the eye may have impaired the circulation enough to cause anterior segment ischaemia in an eye already ischaemic from active occlusive arterial disease. Choroidal infarction following panretinal photocoagulation for proliferative sickle retinopathy has been reported.[37] In this situation the pressure of the contact lens was believed to impair the choroidal circulation.

Concomitant with our patient's retinal arterial occlusive disease was evidence of CNS and systemic disease activity. This supports Gold *et al*'s[3] observation that retinal occlusive disease is associated with CNS and systemic disease activity. SLE patients with active retinopathy should be examined for possible systemic disease activity, so that potentially life threatening complications can be prevented or appropriately treated. In addition SLE patients with retinal arterial occlusive disease should be carefully examined for signs of anterior segment ischaemia. Care should be taken to avoid exacerbating any pre-existing ischaemia when performing operative procedures, including retinal photocoagulation, on these patients. The authors would suggest avoiding any undue pressure on the contact lens, performing panretinal photocoagulation in short, multiple sessions, and if possible avoiding the use of retrobulbar anaesthesia.

References

1 Zvaifler NJ. Etiology and pathogenesis of systemic lupus erythematosus. In: Kelley WN, Harris ED, Ruddy S, *et al.*, eds. *Textbook of rheumatology*. Philadelphia: Saunders, 1981.

2 Gold DH, Morris DA, Henkind P. Ocular findings in systemic lupus erythematosus. *Br J Ophthalmol* 1972; **56:** 800–4.

3 Gold D, Feiner L, Henkind P. Retinal arterial occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol* 1977; **95:** 1580–5.

4 Hall S, Buettner H, Luthra HS. Occlusive retinal vascular disease in systemic lupus erythematosus. *J Rheumatol* 1984; **11:** 846–50.

5 Lanham JG, Barrie T, Kohner EM, Hughes GRV. SLE retinopathy: evaluation by fluorescein angiography. *Ann Rheum Dis* 1982; **41:** 473–8.

6 Vine AK, Barr CC. Proliferative lupus retinopathy. *Arch Ophthalmol* 1984; **102:** 852–4.

7 Cordes FC, Aiken SD. Ocular changes in acute disseminated lupus erythematosus. *Am J Ophthalmol* 1947; **30:** 1541–55.

8 Hammami H, Streiff EB. Alterations vasculaires rétiniennes dans un cas de lupus erythémateux disseminé. *Ophthalmologica* 1973; **166:** 16–35.

9 Pfaffenbach DD, Hollenhorst RW. Microangiopathy of the retinal arterioles. *JAMA* 1973; **225:** 480–3.

10 Coppeto J, Lessell S. Retinopathy in systemic lupus erythematosus. *Arch Ophthalmol* 1977; **95:** 794–7.

11 Graham EM, Spalton DJ, Barnard RO, *et al.* Cerebral and retinal vascular changes in systemic lupus erythematosus. *Ophthalmology* 1985; **92:** 444–8.

12 Girard LJ, Beltranena F. Early and late complications of extensive muscle surgery. *Arch Ophthalmol* 1960; **64:** 576–84.

13 von Noorden GK. Anterior segment ischemia following the Jensen procedure. *Arch Ophthalmol* 1976; **94:** 845–7.

14 Hiatt RL. Production of anterior segment ischemia. *J Pediatr Ophthalmol Strabismus* 1978; **15:** 197–204.

15 Saunders RA, Sandall GS. Anterior segment ischemia syndrome following rectus muscle transposition. *Am J Ophthalmol* 1982; **93:** 34–8.

16 Simon JW, Price EC, Krohel GB, *et al.* Anterior segment ischemia following strabismus surgery. *J Pediatr Ophthalmol Strabismus* 1984; **21:** 179–84.

17 Wilson WA, Irvine SR. Pathologic changes following disruption of blood supply to iris and ciliary body. *Ophthalmology* 1955; **59:** 501–2.

18 Boniuk M, Zimmerman LE. Necrosis of the iris, ciliary body, lens, and retina following scleral buckling operations with circling polyethylene tubes. *Ophthalmology* 1961; **65:** 671–91.

19 Freeman HM, Hawkins WR, Schepens CL. Anterior segment necrosis: an experimental study. *Arch Ophthalmol* 1966; **75:** 644–50.

20 Heyreh SS, Baines JAB. Occlusion of the vortex veins. *Br J Ophthalmol* 1973; **57:** 217–38.

21 Robertson DM. Anterior segment ischemia after segmental episcleral buckling and cryopexy. *Am J Ophthalmol* 1975; **79:** 871–4.

22 Krupin T, Johnson MF, Becker B. Anterior segment ischemia after cyclocryotherapy. *Am J Ophthalmol* 1977; **84:** 426–8.

23 Sharp DC, Bell RA, Cruess AF. Anterior segment necrosis following cyclocryotherapy. *Can J Ophthalmol* 1982; **17:** 268–70.

24 Apple DJ, Craythorn JM, Olson RJ, *et al.* Anterior segment complications and neovascular glaucoma following implantation of a posterior chamber intraocular lens. *Ophthalmology* 1984; **91:** 403–19.

25 Knox DL. Ischemic ocular inflammation. *Am J Ophthalmol* 1965; **60:** 995–1002.

26 Cullis CM, Hines DR, Bullock JD. Anterior segment ischemia: classification and description in chronic myelogenous leukemia. *Ann Ophthalmol* 1979; **11:** 1739–44.

27 Ryan SJ, Goldberg MF. Anterior segment ischemia following scleral buckling in sickle cell hemoglobinopathy. *Am J Ophthalmol* 1971; **72:** 35–50.

28 Eagle RC Jr, Yanoff M, Morse PH. Anterior segment necrosis following scleral buckling in hemoglobin SC disease. *Am J Ophthalmol* 1973; **75:** 426–33.

29 Shearn MA, Pirofsky B. Disseminated lupus erythematosus. Analysis of 34 cases. *Arch Intern Med* 1952; **90:** 790–807.

30 Jessar RA, Lamont-Havers RW, Ragan C. Natural history of lupus erythematosus disseminatus. *Ann Intern Med* 1953; **38:** 717–31.

31 Harvey AM, Shulman LE, Tumulty PA, *et al.* Systemic lupus erythematosus: review of literature and clinical analysis of 138 cases. *Medicine* 1954; **33:** 291–437.

32 Tumulty PA. Clinical course of systemic lupus erythematosus. *JAMA* 1954; **156:** 947–53.

33 Dubois EL, Tuffanelli DL. Clinical manifestations of systemic lupus erythematosus. Computer analysis of 520 cases. *JAMA* 1964; **190:** 104–11.

34 Maumenee AE. Retinal lesions in lupus erythematosus. *Am J Ophthalmol* 1940; **23:** 971–81.

35 Johnson RT, Richardson EP. The neurological manifestations of systemic lupus erythematosus; a clinical-pathological study of 24 cases and review of the literature. *Medicine* 1968; **47:** 337–69.

36 Semon HC, Wolff E. Acute lupus erythematosus, with fundus lesions. *Proc R Soc Med* 1933; **27:** 153–7.

37 Rednam KRV, Jampol LM, Goldberg MF. Scatter retinal photocoagulation for proliferative sickle retinopathy. *Am J Ophthalmol* 1982; **93:** 594–9.

Accepted for publication 27 November 1986.

British Journal of Ophthalmology, 1988, **72**, 17–22

Morphological observations on patients with presumed trichiasis

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SUMMARY The clinical findings in 116 patients with a provisional diagnosis of trichiasis are presented. In 69% a small degree of entropion producing lash-globe contact was detected. The term lid border entropion is proposed for this condition, which is recognised clinically by conjunctivalisation of the meibomian gland orifices and anterior placement of the mucocutaneous junction. These features were clearly demonstrated by electron microscopy of a biopsy specimen from one patient. An analysis of other causes of trichiasis is discussed and an attempt is made to clarify the terminology currently in use.

A number of early descriptions of trichiasis exist, mainly owing to its association with trachoma.[1] The Ebers Papyrus which dates back to the 16th century BC describes it, as did Hippocrates in the 5th century BC. Despite this historical background, trichiasis has no universally accepted specific definition and can be used for a number of eyelid or eyelash abnormalities. Many terms are used to describe it, including: supernumerary lashes, metaplastic lashes, aberrant lashes, pseudocilia, and distichiasis. It is probably best regarded as an 'umbrella term' for conditions characterised by lash-globe contact.

A need exists to describe the morphology of trichiasis and to remove some of the confusion on its terminology. We present here a study of the clinical characteristics and morphology of a group of patients with presumed trichiasis.

Patients and methods

One hundred and sixteen patients regularly attending an ophthalmic unit with a provisional diagnosis of trichiasis were entered into the study. They were all undergoing intermittent epilation by nursing staff or specific treatment by medical staff.

Most of the patients attended on a casual basis without appointment and, to estimate the demand at the unit for treatment, details of their age, duration of symptoms, and attendance rates were compiled. Each patient was examined and photographed. Face and eyelid photographs were taken to show anatomical details and to provide an accurate record.

Results

The age of the patients varied from 20 to 89 years, with an average of 64 years. The onset of trichiasis for each patient was noted and a histogram compiled. The onset of trichiasis was maximal between the ages of 60 and 70 years (Fig. 1). The average duration for trichiasis in this group of patients is shown in Fig. 2: 58% had suffered from trichiasis for five years or more and 15% for 30 years or more. The patients were attending an ophthalmic casualty, usually for epilation on a regular basis by nursing staff; 40%

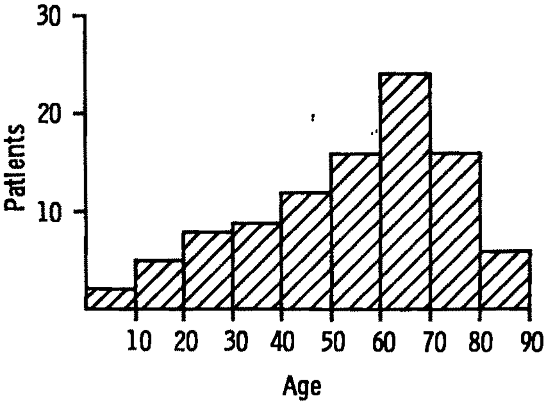

Fig. 1 *Age distribution of patients at onset of trichiasis.*

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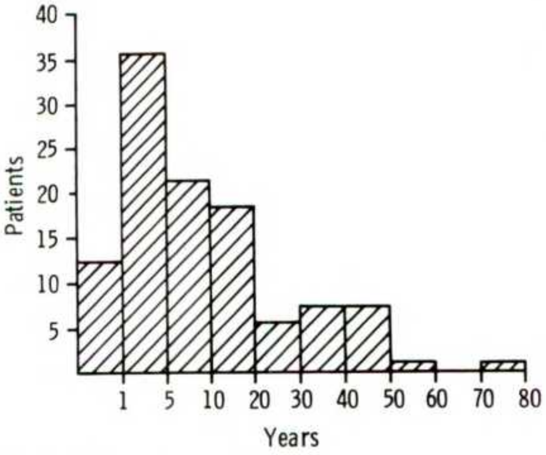

Fig. 2 *Duration in years of trichiasis.*

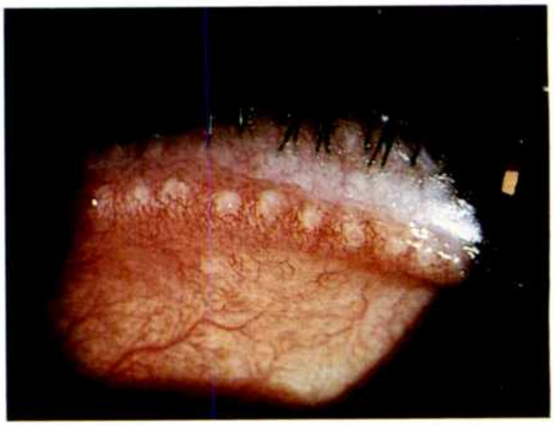

Fig. 3 *Upper eyelid with conjunctivalisation of meibomian gland orifices.*

were attending between one and four times per month. The average rate of attendance was once every 7·5 weeks, and this resulted in approximately 10 patient visits per week.

Table 1 shows the distribution of morphological changes seen in this group of 116 patients. Seven patients (6%) who regularly attended for epilation by nursing staff complained of irritation and believed that this was due to trichiasis. On successive slit-lamp examinations these patients had no evidence of lash-globe contact despite their symptoms.

The remaining 109 patients could be divided into

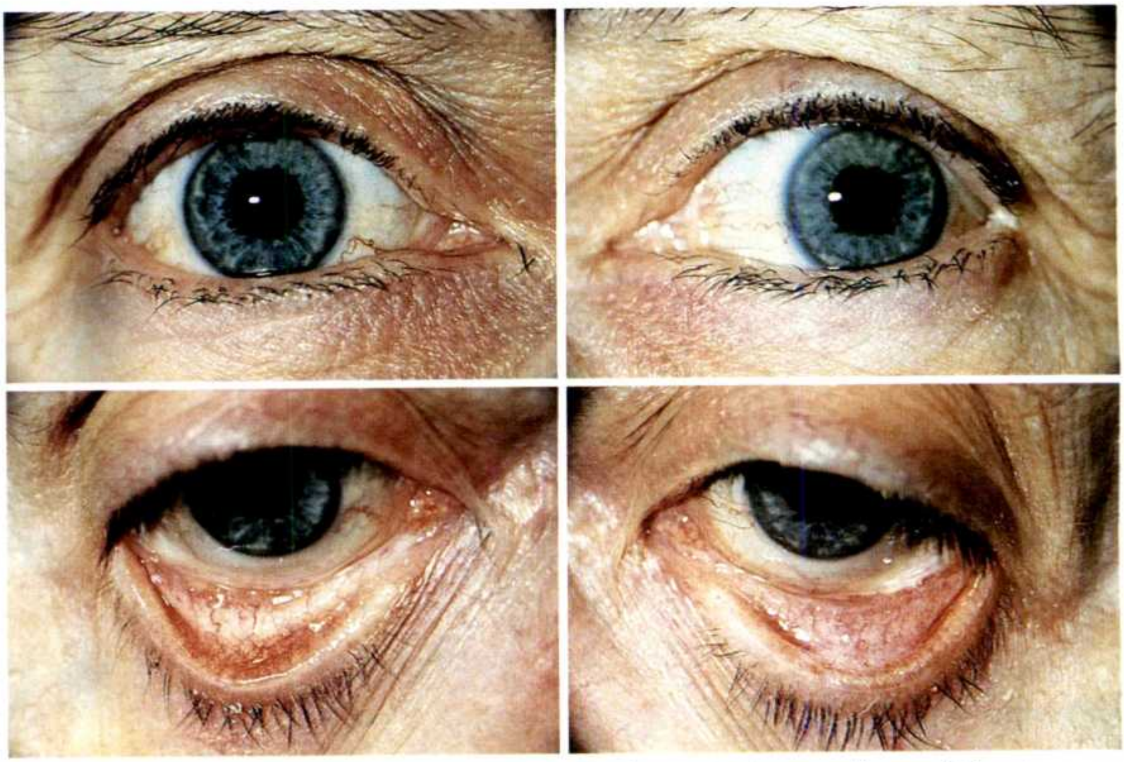

Fig. 4 *Left lower lid trichiasis with conjunctival scarring and lid border entropion (compare with normal right eye).*

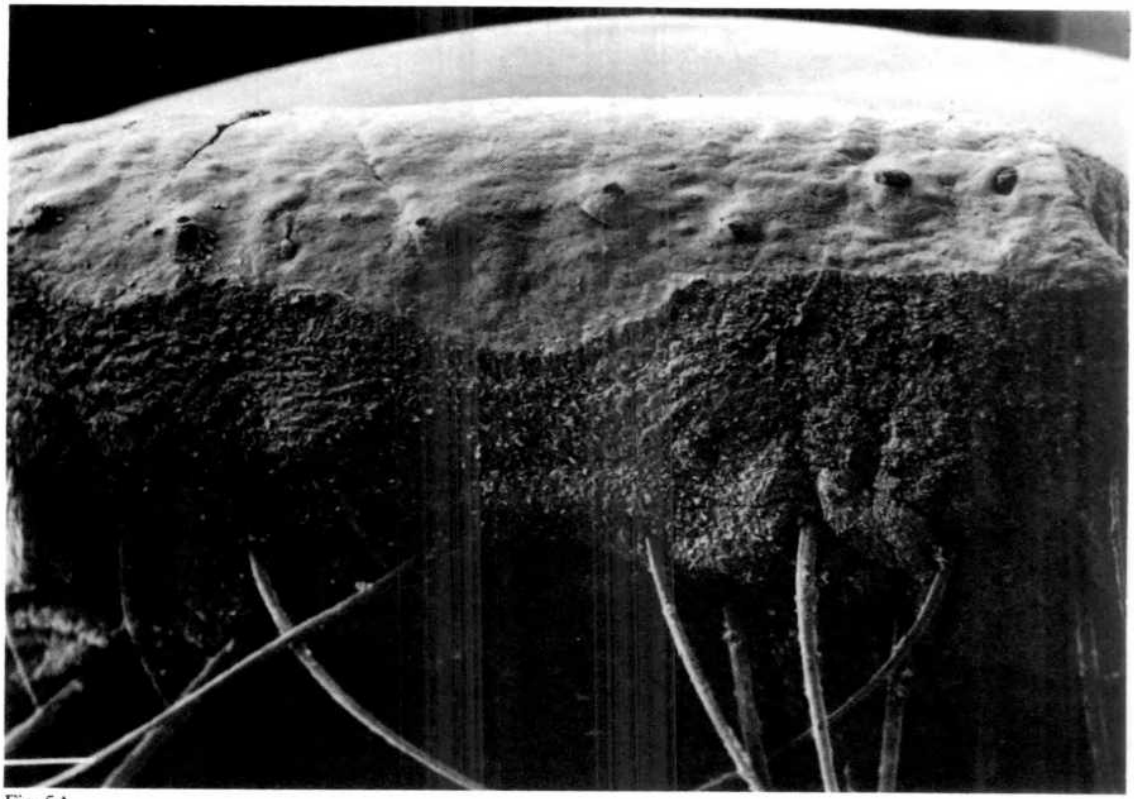

Fig. 5A

Fig. 5A: *Scanning electronmicrograph of a block of eyelid from a patient with lid and border entropion. The mucocutaneous junction is seen between the meibomian gland orifices and the lash line.* B: *Mucocutaneous junction showing division between squamous epithelium and conjunctival epithelium.* C: *Microvilli on conjunctival epithelium.*

those patients with eyelash abnormalities causing lash-globe contact and those with eyelid abnormalities doing so. Only 14 patients had purely eyelash abnormalities. The great majority of patients (95) had eyelid abnormalities causing lash-globe contact. Seven patients had misdirection of lashes that were causing lash-globe contact, with an otherwise normal eyelid margin. Misdirected lashes were seen together with lid border entropion in 29 patients and in association with lid margin notch in 16 patients. Misdirected lashes are therefore commonly seen in trichiasis but are usually associated with other eyelid abnormalities rather than existing on their own.

Table 1 *Anatomical abnormalities seen in 116 patients*

No abnormality		7
Eyelash abnormalities:	Misdirected	7
	Metaplastic	3
	Distichiasis	1
	Malposition	3
Eyelid abnormalities:	Lid border entropion	78
	Lid border entropion and lid notch	2
	Lid margin notch	15

Distichiasis (defined as a congenital row of lashes arising from the meibomian gland orifices) was seen in only one patient. Metaplastic lashes (defined as an acquired row of lashes arising from the meibomian gland orifices) were seen in three patients. Another three patients had an extension of the normal eyelash line medially and laterally involving the canthal regions. Recognising this as a cause of trichiasis is probably not justified.

In 95 patients (82%) a lid abnormality was present. Seventeen patients had lid margin notches secondary to temporary tarsorrhaphy or removal of a lid tumour. In these patients a normal lash line was present except in the notched area, where distortion of the follicles resulted in misdirected lashes.

The most common lid abnormality consisted of a small degree of entropion, which we refer to as lid border entropion. This condition was identified by conjunctivalisation of the meibomian gland orifices

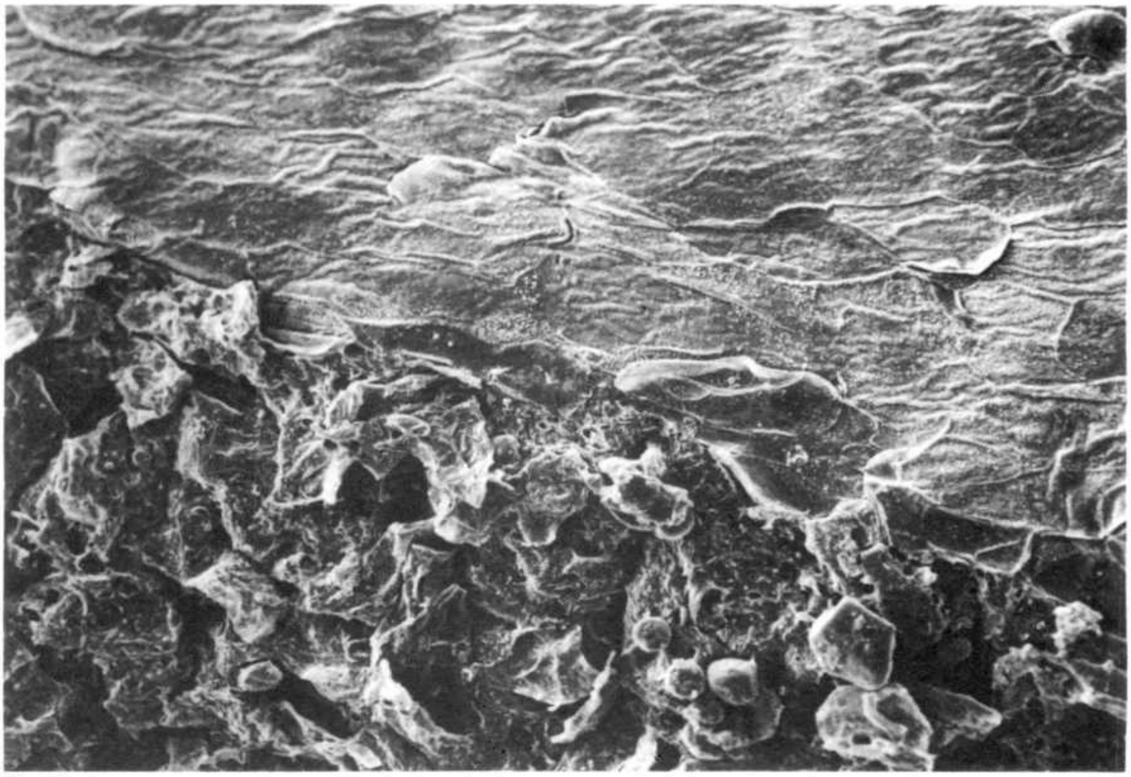

Fig. 5B

and anterior placement of the mucocutaneous border of the lid (Fig. 3).

This is distinguishable from established involutional lower lid entropion in that it is neither intermittent nor invoked by forced closure of the eyelids. Fig. 4 shows lid border entropion (left eye) with lash globe contact. In this case conjunctival scarring has caused the lid border entropion.

Scanning electron microscopy was used to demonstrate the position of the mucocutaneous junction in lid border entropion and to establish the nature of the epithelium at the lid margin in this condition. A corrective pentagon excision was performed on one patient with lid border entropion. Figs. 5A, B, C show the lid margin of this patient. The mucocutaneous junction is well anterior to the meibomian gland orifices; normal conjunctival epithelium with microvilli surrounds the meibomian gland orifices, and the mucocutaneous junction is well demarcated with squamous epithelium in juxtaposition with conjunctival epithelium. There is no apparent transition zone.

Eighty patients (69%) had lid border entropion which caused lash-globe contact (Table 2). This was seen in association with conjunctival scarring in 41 patients. These patients were thought, therefore, to have a cicatricial lid border entropion. Thirty-nine patients had lid border entropion without any evidence of conjunctival scarring. This has been termed involutional lid border entropion.

Table 2 *Types of lid border entropion in 80 patients with trichiasis*

Cicatricial upper lid border entropion	17
Cicatricial lower lid border entropion	17
Cicatricial upper and lower lid entropion	7
Involutional lower lid border entropion	17
Involutional upper lid border entropion	22

Discussion

A certain amount of confusion exists regarding the terminology pertaining to trichiasis. Trichiasis is derived from the Greek for hair, and is generally used to denote irritation caused by lash-globe contact. Many associated terms are used to describe the various forms of trichiasis, some of which are helpful and others confusing.

Distichiasis has been well described.[2-9] It is a congenital condition whereby a second row of lashes exists along the posterior border of the lid margin

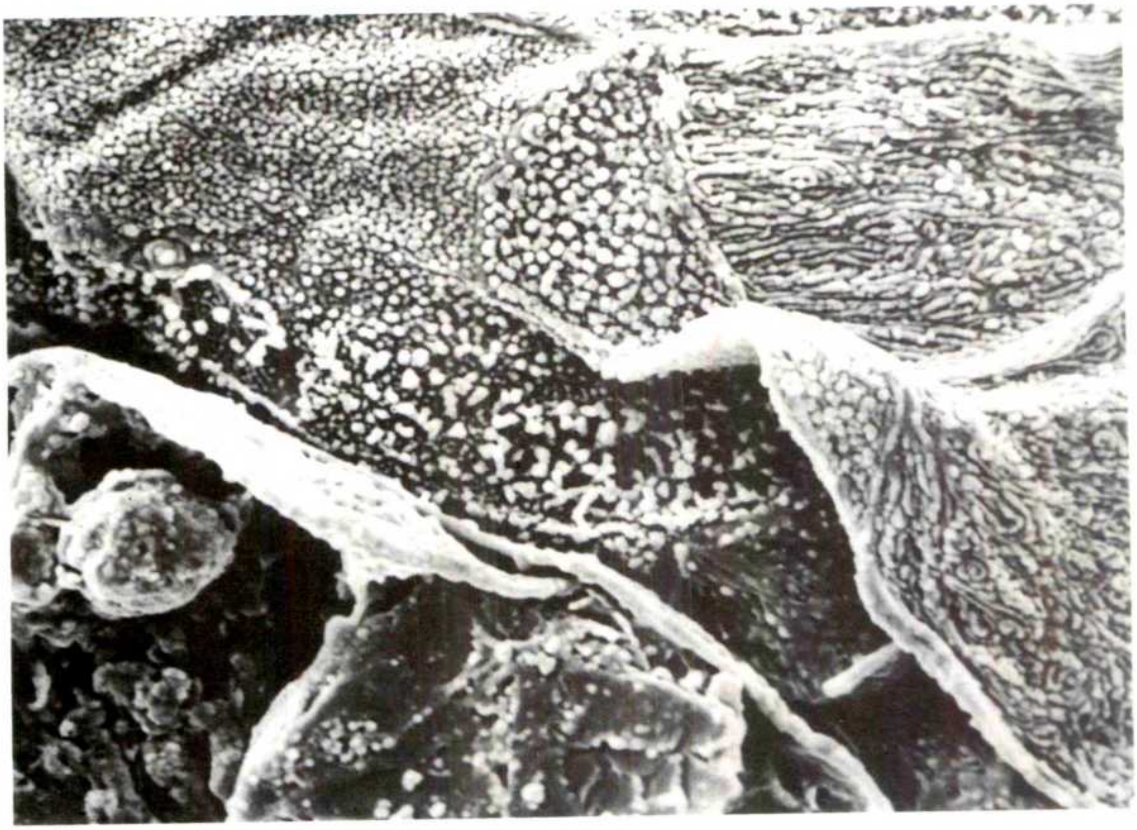

Fig. 5C

in the position of the meibomian gland orifices. Histology of such eyelids has shown lack of meibomian glands.[2,6,7] The meibomian glands are pilosebaceous units in which hair development is absent.[4,10] Failure of differentiation of the pilosebaceous unit results in lashes arising from the meibomian gland region and is regarded as a form of atavism by some.[8]

Under certain circumstances the meibomian glands may revert back to the hair-bearing state of the pilosebaceous unit, and this would then constitute a metaplastic change. It is sensible, therefore, to call these metaplastic lashes. They are seen in association with the late stages of Stevens-Johnson syndrome, in which other metaplastic changes such as keratinisation of the tarsal conjunctiva occur. (Both distichiasis and metaplastic lashes were seen infrequently in this study.)

Misdirected lashes were frequently seen in this study (45%). However, they infrequently cause trichiasis by themselves in an otherwise normal eyelid (6%). 14% of patients had misdirected lashes in combination with lid margin defects. These patients had undergone opening of tarsorrhaphy or tumour removal which involved the lash line without adequate reconstruction of the lid margin.

The majority of patients (69%) in this study have a small degree of entropion of the lid border. Duke-Elder[1] mentioned this in passing but did not define it, and Duane expressed difficulty in diagnosing entropion in patients with trichiasis.[11] Collin[12] and Jones *et al.*[13] described the early changes of upper lid entropion as an apparent migration of the meibomian gland orifices and conjunctivalisation of the lid margin. This study shows that the entity we refer to as lid border entropion is frequently seen in patients with trichiasis. Clinically it is recognised by the presence of conjunctiva surrounding the meibomian gland orifices, with an abnormal anterior displacement of the mucocutaneous junction. The meibomian gland orifices are easily seen and seem to be prominent when surrounded by conjunctiva. This may be due to the presence of stratified squamous epithelium in the meibomian gland openings, which contrasts with the surrounding conjunctival epithelium.

It is believed that a metaplastic change occurs in surface epithelium, changing keratinised squamous epithelium into conjunctival epithelium with micro-

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villi. The stimulus for this change in lid border entropion is presumably the presence of the tear film. Scanning electron microscopy demonstrates that in lid border entropion the mucocutaneous junction lies between the meibomian gland orifices and the lash line. Interestingly the situation in ectropion has been shown to be entirely the reverse, with a metaplastic change from tarsal conjunctiva to keratinised epithelium taking place posterior to the meibomian gland openings.[14]

It is apparent that the surface epithelium at the lid margin has potential for metaplastic change, and this is influenced by the position of the tear film relative to the lid margin structures. More precise identification of the factors influencing epithelial morphology would be of value in increasing our understanding of those conditions in which metaplasia of the conjunctiva is a prominent and potentially blinding feature.

We thank Miss M A C Jones, Mr C A L Palmer, Mr I M Strachan, and Mr J F Talbot for providing patients for this study. We also thank Mr I G Rennie and Dr A Parsons for their help with electron microscopy.

References

1 Duke-Elder S. *Textbook of ophthalmology*. St Louis: Mosby, 1952: 5: 383–5.
2 Fox SA. Distichiasis. *Am J Ophthalmol* 1962; 53: 13–8.
3 Duke-Elder S. *Textbook of ophthalmology*. St Louis: Mosby, 1952; 3: 873–5.
4 Anderson RL, Harvey JT. Lid splitting and posterior lamellar cryosurgery for congenital and acquired distichiasis. *Arch Ophthalmol* 1981; 99: 631–4.
5 Kuhnt E. Ueber distichiasis congenita vera. *Z Augenheilkd* 1899; 2: 46–57.
6 Brailey AR. Congenital distichiasis. *Trans Ophthalmol Soc UK* 1906; 26: 16–22.
7 Pico S. Congenital ectropion and distichiasis: actiologic and hereditary factors. A review of the literature. *Am J Ophthalmol* 1959; 47: 363–87.
8 Scheie HG, Albert DM. Distichiasis and trichiasis: origin and management. *Am J Ophthalmol* 1966; 61: 718–20.
9 Last RJ. *Eugene Wolff's anatomy of the eye and orbit.* Philadelphia: Saunders, 1961: 171–2.
10 Wood JR, Anderson R. Complications of cryosurgery. *Arch Ophthalmol* 1981; 99: 460–3.
11 McCord CD. In: Duane T, ed. *Clinical ophthalmology*. Hagerstown: Harper Row, 1983: 5: chapter 5: 16–7.
12 Collin JRO. *A manual of systematic eyelid surgery*. Edinburgh: Churchill Livingstone, 1983: 16.
13 Jones BR, Baulas TC, Hunter PA, Darougar S, Mohsenine H. Neglected lid deformities causing progressive corneal disease. *Trans Ophthalmol Soc UK* 1976; 96: 45–51.
14 Stefanyszyn MA, Hidayat AA, Flanagan JC. The histopathology of involutional ectropion. *Ophthalmology* 1985; 92: 120–7.

Accepted for publication 4 December 1986.

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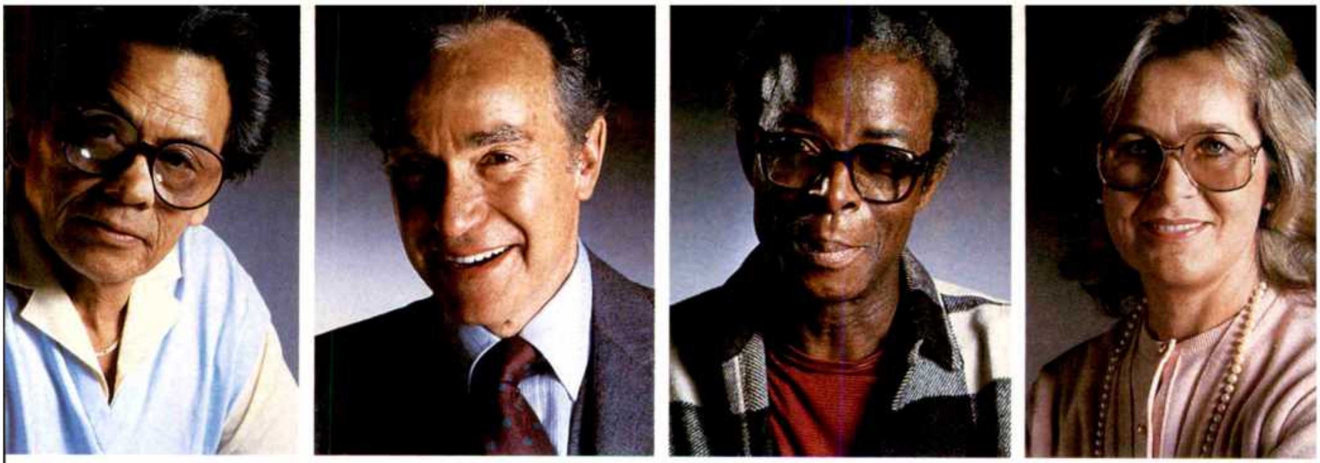

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References

1. Zimmerman, T. J., presented at: Int. Symposium on Glaucoma, XIII Int. Congress of Ophthalmology, Kyoto, Japan, May 1978, 55-64.
2. Sponsel, W. E., *et al., Brit. J. Ophthal.*, 1983, **67**, 220-227.
3. Sponsel, W. E., International Symposium on Glaucoma, Turin, 1986.
4. Katz, I. M., presented at: Int. Symposium on Glaucoma, XIII Int. Congress of Ophthalmology, Kyoto, Japan, May 1978, 29.

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Ocular quinine toxicity

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SUMMARY A case of ocular quinine toxicity is described which showed the typical acute visual loss and subsequent recovery. Vermiform motion of the pupil was noted 48 hours after overdose. This acute effect has not been reported before. Although acute systemic intoxication may respond to removal of quinine from the gut and circulation, there is no evidence that any treatment affects the visual prognosis. The action of quinine on the retina is unknown. We suggest it may block cholinergic neurotransmission in the inner synaptic layer.

Quinine is one of the few drugs which has altered the course of history. The activity it has against malaria allowed the habitation of large parts of the globe. Quinine toxicity is still a problem today,[1 2] but little progress has been made in defining the mechanism of its retinal toxicity. We present a case of quinine overdose and speculate on a possible way in which it may affect the retina.

Case history

A 28-year-old woman presented one morning 12 hours after ingesting 9 g of quinine sulphate in an attempt to commit suicide. Within two hours of taking the tablets she had vomited. She noticed tinnitus, fluctuating deafness, rapid palpitations, and paraesthesia on her face. She did not become aware of visual symptoms until the morning, when she awoke totally blind. She was otherwise in good health. The quinine had been prescribed for foot cramps of unknown cause. She had had no previous eye disease.

She was transferred to Moorfields Eye Hospital that day. Twenty-four hours after the overdose the corrected vision was 6/18 right and 6/12 left. Both pupils had a diameter of 9 mm in ambient light and reacted slowly to light and accommodation. There was no relative afferent pupil defect. The intraocular pressures were normal. There was retinal oedema at the posterior poles, and the retinal vessels were engorged.

The serum quinine level was measured on three occasions. Sixteen hours after the overdose it was 8·2 mg/l, at 20 hours it was 6·4 mg/l, and at 48 it was 3·1 mg/l. A forced acid diuresis had been started at the referring hospital. This was discontinued and no other treatment was given.

Her visual fields on the first day in hospital were markedly constricted. They improved progressively over two months until they were almost normal. The Farnsworth Munsell 100-hue test (Fig. 1) remained grossly abnormal over two months. No specific pattern of dyschromatopsia was identified. The central acuity improved over the two months to 6/9

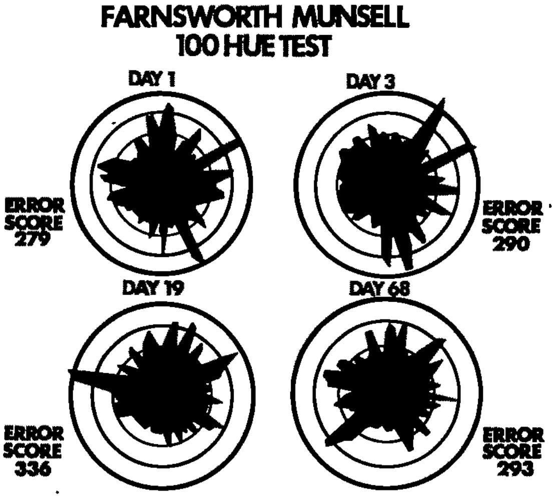

Fig. 1 *The Farnsworth-Munsell 100 hue test was done under the same lighting level and with the same test set on each occasion. The time scale refers to the number of days elapsed from taking the overdose.*

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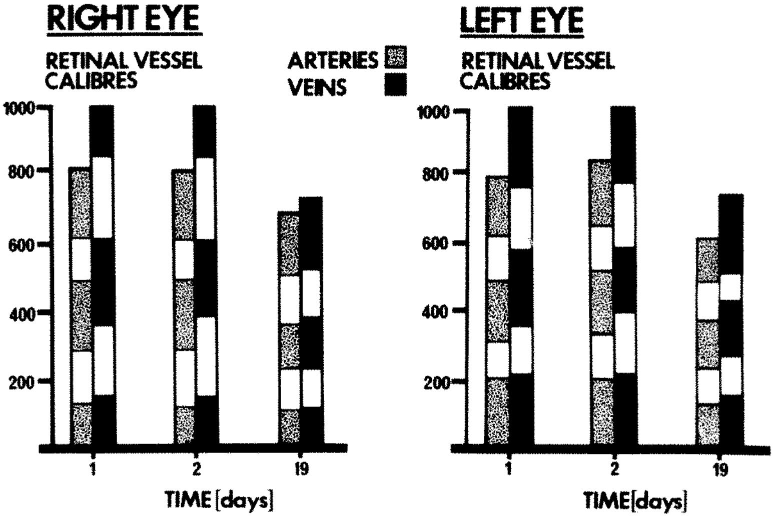

Fig. 2 *Retinal vessel calibres: the y axis scale is the diameter in µm of the vessels measured on retinal photographs. Five points were selected on veins and five on arteries in each eye which could reliably be identified on serial photographs. The bars are the cumulative diameters at these five points. The x axis time is the number of days elapsed from taking the overdose.*

right and left, and the retinal oedema resolved. The retinal vessels became attenuated, and optic disc pallor developed.

Retinal vessel calibres were measured by an image analysis method developed at the Royal College of Surgeons of England (Fig. 2). Red-free fundus photographs were taken in mid-diastole with a Canon wide-angle fundus camera. The blood pressure and intraocular pressure were recorded. Vessel calibres were measured on the photographs at several sites chosen where they could be identified on serial photographs.

Vermiform pupil motion was noted in both eyes on the day after the overdose. It persisted for the duration of follow-up. Instilling 0·125% pilocarpine drops into one eye produced a brisk miosis.

Electrophysiological studies were done on day 1 and repeated several times, the last being day 66. The electroretinogram (ERG) done on day 1 showed a normal amplitude to blue, red, and white stimuli, though the oscillatory potentials were reduced. The response to flicker was delayed and abnormal. The pattern ERG was markedly reduced, and no pattern visual evoked response (VER) could be recorded. A flash VER did show a small response with a normal latency. The visual acuity at that time was 6/18 right and 6/24 left, with a markedly constricted visual field and normal retinal vessel calibres.

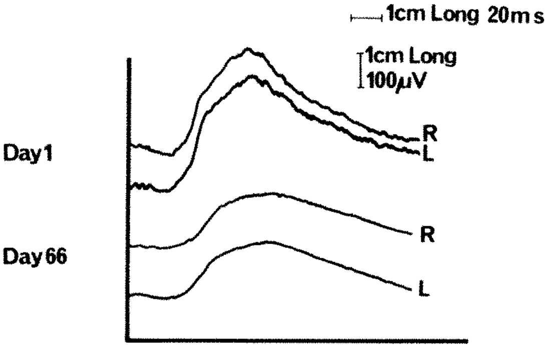

Fig. 3 *Electroretinogram: the flash ERG to blue light under scotopic conditions done on day 1 and day 66.*

Subsequently, the ERG amplitude became reduced (Fig. 3). The abnormal flicker response and pattern ERG persisted. A pattern VER was recordable for high contrast gratings, but with an increased latency. A dark adaptation test was attempted on one occasion but could not be interpreted owing to large variations in the response.

Discussion

This case is quite typical of quinine overdose. Early in the course, when the visual acuity was poor, the retinal vessel calibre looked normal. As the vision improved the vessels became attenuated and disc pallor developed. Smith, in 1919, called this the 'paradox of quinine'.[3] The role of vessel calibre changes in the pathogenesis of visual impairment is still uncertain.[1 2 4-12]

TREATMENT OF RETINAL QUININE TOXICITY

This patient received no treatment apart from a brief forced acid diuresis. The wide range of remedies that have been tried in this condition, ranging from strong coffee[13] to haemoperfusion,[14] reflect both the physician's desire to do something in the face of the usually dramatic loss of vision and the current lack of understanding of the pathogenesis of this form of blindness. Treatments are aimed either at reducing the serum quinine level or at preventing or reversing retinal vessel spasm.

The serum quinine level can be reduced by inhibiting quinine absorption from the gut, and perhaps by measures to remove it from the circulation or promote its excretion in the urine. Activated charcoal, if given early, can reduce absorption from the gut. Quinine otherwise is rapidly absorbed, and the serum level reaches a peak in one to three hours.[10] Most quinine is excreted in the urine.[14] It has long been held that urinary excretion can be facilitated by forced acid diuresis, that haemodialysis can produce a rapid drop in serum level, and that plasmapheresis can remove the protein-bound fraction of the serum quinine (about 70%). Recent work has challenged all these assumptions,[15] however, and the subject is controversial.

The methods advocated for dilating the retinal vessels include various vasodilators given orally, parenterally, and within the orbit; massage of the globe; paracentesis; carbon dioxide inhalation; recumbent posture; and stellate ganglion blockade.[7] No paper has yet shown that any of these methods offers a better visual prognosis than not treating the patient at all. Some methods, such as stellate ganglion block, have a considerable morbidity.[16] Therefore, while life threatening systemic toxicity must be treated, treatment aimed purely at the visual loss is more difficult to justify.

VERMIFORM PUPIL MOTION

This patient displayed vermiform motion of the pupils with enhanced sensitivity to 0·125% pilocarpine drops within 48 hours of the overdose. Hippus was reported in several early papers,[13 17] which may actually have been vermiform motion. A case of tonic pupil with denervation supersensitivity has been reported in a patient 10 months after overdose.[18] This does not appear to have been noted as an early feature of quinine toxicity, however.

The effect may be due to damage to the parasympathetic nerves supplying the iris, to the neuromuscular junction, or to the sphincter pupillae itself. Quinine has a curare-like action,[10] and so perhaps inhibition of acetylcholine release at the neuromuscular junction may promote the 'denervation supersensitivity' suggested by the miosis to 0·125% pilocarpine.

Quinine is also an irritant drug which has been used as a sclerosing agent in the past. It may damage the vessels supplying the iris. This is thought to be responsible for the iris atrophy seen in some cases.[18] Acute ischaemia of either the sphincter muscle or its nerve supply may have produced the abnormal pupil response.

PATHOGENESIS OF RETINAL TOXICITY

The mechanism of the toxic action of quinine is unknown. The dramatic initial visual loss is not due to retinal ischaemia, since the vessel calibres at that time are normal. The drug must therefore affect the retinal neurones directly. Most electrophysiological studies on patients, including our own, have been done more than 12 hours after the overdose, and the ERG at that time may be normal. The ERG then becomes progressively more abnormal for at least three weeks.[9]

Typically the a-wave deepens and the b-wave shrinks. The photopic component is affected more than the scotopic. Oscillatory potentials are absent, and the flicker response is reduced or absent. The severity of the changes broadly correlate with the degree of visual impairment. These findings suggest that the outer retinal elements are less affected than the bipolar cells.[9] Similar ERG findings have been observed following central retinal artery occlusion.

A normal early ERG in the presence of severe visual dysfunction suggests that quinine must affect an 'electrically silent' part of the retina initially, such as ganglion cells, which do not contribute to the flash ERG waveform. Moreover the abnormal pattern ERG and reduced oscillatory potentials during the same period, such as was noted in our patient, support the view that the inner retina is mostly affected. Often the only visible abnormality in the fundus at this time is nerve fibre layer oedema, and there is some histological evidence showing damage to this layer.[4]

Two observations have challenged the central role of ganglion cell toxicity in acute quinine blindness. Several workers have now found that the ERG within the first 12 hours of the ingestion of quinine may not be normal.[8 19] In experimental models the ERG changes within minutes of quinine administration—the a-wave deepens and the b-wave reduces, and this reverts to normal within 24 hours.[8] Similar findings have been reported in a few patients.[19] This may represent a global retinal toxicity from quinine in its role as a 'general protoplasmic poison'.[10] The fact remains that patients are blind with normal flash ERG recordings, however, so more specific inner retinal toxicity must also occur.

The second observation is that the electroculogram (EOG) is grossly abnormal, with no light rise, in the acute phase of quinine toxicity.[18–20] It reverts to normal later and may parallel the course of the visual impairment. This is interpreted as a loss of function at the photoreceptor/pigment epithelium level.[20] Henkes and Deutman[21] noted that both the EOG and the a-wave of the ERG depend on photoreceptor function, however, and that an as yet unexplained discrepancy exists between the abnormal EOG and normal flash ERG in acute quinine toxicity. It seems quite likely, therefore, that both the outer and inner retinal layers are affected.[18]

Quinine may possibly act as an antagonist of a neurotransmitter. If this is so, acetylcholine is most likely to be affected, for several reasons:

(1) Quinine has a curare-like action on neuromuscular junctions.[10] The action can be competitively antagonised by neostigmine. It also has other anticholinergic actions such as mydriasis and sinus tachycardia.

(2) The inner synaptic layer of the retina, where quinine may be acting, stains heavily for acetylcholinesterase,[22] indicating that acetylcholine is present in the layer. It is one of at least five proposed neurotransmitters in the inner synaptic layer, together with gamma amino butyric acid (GABA), glycine, dopamine, and serotonin.[23]

(3) Ganglion cells are thought to be cholinoreceptive neurones. Electrophoretically applied acetylcholine excites off-cells and inhibits on-cells. Some workers[23] have suggested that the effects of acetylcholine are mediated via nicotinic receptors and can be blocked by curare. Quinine, with its known curare-like action, may act here.

(4) A subpopulation of amacrine cells also probably synthesises acetylcholine as a neurotransmitter.[23] Iontophoretic application of acetylcholine suggests that these cells stimulate phasic ganglion cells. Quinine again may block this action.

(5) Almeida[5] notes that Giannini[24] found simultaneous administration of quinine and acetylcholine to dogs can prevent the toxic effects of quinine on the retina.

Quinine may produce acute blindness by interfering with cholinergic neurotransmission in the inner synaptic layer. If this is the mechanism of action, it may be possible to modify it pharmacologically. This acute visual loss, however, will usually at least partly recover. The component of visual loss which is permanent most needs treatment. It is even now not possible to say whether this is the result of irreversible acute retinal toxicity or secondary to retinal vascular insufficiency. Future studies will need to address this problem.

The authors thank Mr J Kelsey for suggestions about the effects of quinine, Dr J Henry for referring the case, and Professor D W Hill for his help and encouragement. Miss S Hague was supported by an award from the Smith and Nephew Foundation.

References

1 Boland ME, Brennand Roper SM, Henry JA. Complications of quinine poisoning. *Lancet* 1985; i: 384–5.

2 Dyson EH, Proudfoot AT, Prescott LF, Heyworth R. Death and blindness due to overdose of quinine. *Br Med J* 1985; **291:** 31–3.

3 Smith HE. Quinine amaurosis. *Trans Ophthalmol Soc UK* 1919; **39:** 310–6.

4 de Schweinitz G. Additional experiments to determine the lesion in quinine blindness. *Trans Am Ophthalmol Soc* 1891; **6:** 23–9.

5 Almeida H. Quinine amblyopia. *Quarterly Bulletin of the Northwest University Medical School* 1961; **35:** 217–22.

6 Brinton GS, Norton EWD, Zahn JR, *et al.* Ocular quinine toxicity. *Am J Ophthalmol* 1980; **90:** 403–10.

7 Bard LA, Gills JP. Quinine amblyopia. *Arch Ophthalmol* 1964; **72:** 328–31.

8 Cibis GW, Burian HM, Blodi FC. Electroretinogram changes in acute quinine poisoning. *Arch Ophthalmol* 1973; **90:** 307–9.

9 François J, De Rouck A, Cambie E. Retinal and optic evaluation in quinine poisoning. *Ann Ophthalmol* 1972; **4:** 177–85.

10 Goodman LS, Gillman A. *The pharmacological basis of therapeutics.* 4th ed. London: Collier MacMillan, 1970: 1115–24.

11 Grant WM. *Toxicology of the eye.* 2nd ed. Springfield, Illinois: Thomas, 1974: 870–6.

12 Walsh FB, Hoyt WF. *Clinical Neuro-ophthalmology.* 3rd ed. Baltimore: William and Wilkins, 1969: 2552–5.

13 Duggan JN, Nanavati BP. Two cases of quinine amblyopia with unusual ophthalmoscopic pictures. *Br J Ophthalmol* 1931; **15:** 160–4.

14 Dickinson P, Sabto J, West RH. Management of quinine toxicity. *Aust J Ophthalmol* 1983; **11:** 265–9.

15 Bateman DN, Blain PG, Woodhouse KW, *et al.* Pharmacokinetics and clinical toxicity of quinine overdosage: lack of efficacy of techniques intended to enhance elimination. *Q J Med* 1985; **54:** 125–31.

16 Adriani J, Parmely J, Ochsner A. Fatalities and complications following attempts at stellate ganglion block. *Surgery* 1952; **32:** 615–9.

17 Orr RG. Quinine amblyopia. *Br J Ophthalmol* 1946; **30:** 766.

18 Gangitano JL, Keltner JL. Abnormalities of the pupil and visual evoked potential in quinine amblyopia. *Am J Ophthalmol* 1980; **89:** 425–30.

19 Hommer K. Über die Chininvergiftung der Netzhaut. *Klin Monatsbl Augenheilkd* 1968; **152:** 785–805.

20 Behrman J, Mushin A. Electrodiagnostic findings in quinine amblyopia. *Br J Ophthalmol* 1968; **52:** 925–8.

21 Henkes HE, Deutman AF. Electrodiagnostic procedures in drug-induced ocular diseases. *Doc Ophthalmol* 1973; **34:** 209–19.

22 Moses RA. *Adler's physiology of the eye.* St Louis: Mosby, 1981: 390–1.

23 Pycock CJ. Retinal neurotransmission. *Surv Ophthalmol* 1985; **29:** 355–65.

24 Giannini D. Dell' influenza dei disturbi di circolo sulla patogenesi della alterazioni funzionali ed anatomiche del nervo ottico e della retina negli avvelenamenti da chinino. *Ann Ottalmol Clin Oculist* 1934; **62:** 1069.

Accepted for publication 27 November 1986.

British Journal of Ophthalmology, 1988, **72**, 27–28

A double-crossover trial comparing the effects of topical carteolol and placebo on intraocular pressure

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SUMMARY The effect of topical carteolol 2% on the intraocular pressures of 12 patients suspected of having glaucoma was measured in a double-crossover trial of six weeks' duration. Carteolol produced a significant reduction in intraocular pressure ($p \leq 0 \cdot 001$), when compared with placebo. This represented reductions of 11% and 14%, after one and two weeks of treatment.

Recently introduced as treatment for raised intraocular pressure, carteolol is a non-selective beta-blocking agent with some intrinsic sympathomimetic activity. Previous placebo controlled studies[1-3] are single-dose studies, and are discussed below. In this placebo controlled crossover study we demonstrated that topical carteolol 2%, administered twice daily for two weeks, produced a significant reduction in intraocular pressure.

Patients and methods

Twelve subjects (nine female and three male) with normal visual fields were recruited from a glaucoma clinic. These subjects were thought to be at risk of developing glaucoma because of raised intraocular pressures, a family history of glaucoma, or cupping of their optic discs. Exclusion criteria were: confirmed open angle or closed angle glaucoma, any visual field defect, visual acuities of less than 6/12, corneal disease, a history of ocular surgery, asthma, chronic obstructive airways disease, cardiac failure, renal dysfunction, or current therapy with a beta-blocking agent.

Ethical approval was obtained from the hospital ethics committee. All subjects gave written informed consent, and underwent a pretrial physical examination and electrocardiograph. All subjects had their visual fields checked by a Goldmann perimeter (Armaly technique[4]) to ensure that they were normal. Those on ocular hypotensive treatment had their case histories and visual fields reviewed by an independent observer before their medication was stopped at least two weeks prior to the trial.

The subjects were randomly allocated to two groups of six subjects each. There was a two-week treatment period followed by a two-week washout, then a final two-week treatment period. The subjects instilled drops in each eye twice daily throughout the trial. The subjects in group 1 were given carteolol 2% to the right eye and placebo drops to the left eye for two weeks, then placebo to both eyes for two weeks, then two weeks with placebo to the right eye and carteolol to the left eye. The subjects in group 2 were given the treatments in reverse order.

Intraocular pressures were measured at baseline and then weekly for six weeks. The intraocular pressure measurements were made by the same investigator at the same time of day (to within 20 minutes) approximately six to eight hours after treatment. All subjects completed the study. There were no withdrawals due to adverse effects, though soon after the onset of the trial one subject reported an episode of 'wheezing' which lasted 20 minutes.

Paired t tests were used to confirm that there was no difference between the initial intraocular pressures of groups 1 and 2. The difference between right and left eyes, and the difference between the eyes about to receive carteolol or placebo, did approach significance ($p=0 \cdot 064$ and $p=0 \cdot 093$, respectively), and this was therefore taken into consideration in the analysis of the results. The effectiveness of the washout period was confirmed by paired t tests, as outlined by Hills and Armitage.[5]

In the crossover analysis the results for weeks 1 and 5 (or weeks 2 and 6) were compared. If symmetry of effect between the right and left eyes is not taken for granted, the sum of the effects in the two treatment periods was calculated—that is, $(R1-L1)-(R5-L5)$ for each subject, where R1 is the intraocular pressure in the right eye for a given subject at the end of week one, and so on. The two groups were then compared

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Table 1 *Comparison of IOP between carteolol and placebo in 12 subjects, with allowance for possible asymmetry between eyes. Mean pretreatment IOP (±SE) for 12 subjects was 21 (±1·2) mmHg*

Weeks to be compared	*df*	*Estimated difference in IOP, carteolol minus placebo*	*95% confidence limits*	*t*	*p*
1 and 5	10	−1·17	−1·78 to 0·55	−4·24	0·001
2 and 6	10	−2·08	−2·70 to −1·47	−7·57	<0·001
1 adjusted for 0	9	−2·82	−4·03 to −1·61	−5·29	<0·001
2 adjusted for 0	9	−2·16	−3·70 to −0·62	−3·18	<0·01

by a 2-sample *t* test (10 df); similarly for weeks 2 and 6.

Results

Carteolol 2% produced a significant reduction in intraocular pressure. Whether the data for weeks 1 and 5 or those for weeks 2 and 6 are analysed, the results were qualitatively the same. If only the first treatment period is considered, a significant result was still obtained. In this case the difference between carteolol and placebo was 2·82 mmHg for week 1, and 2·16 mmHg for week 2, which represent reductions of 14% and 11% respectively. The mean (±SE) pretreatment intraocular pressure for all 12 subjects was 20·7 (±1·15) mmHg. The results are summarised in Table 1.

Discussion

In the present study the subjects received active treatment to one eye and placebo to the other. After a washout period the treatments were reversed. This double-crossover design does make the study an extremely efficient one, though the assumption is made that carteolol has no significant effect on the contralateral placebo treated eye. Any such effect will tend to decrease the apparent treatment effect, so that both our estimated difference between active and placebo and its significance levels are conservative.

We obtained reductions in intraocular pressure of 14% and 11% after one and two weeks' treatment. This is in close agreement with Horie *et al.*,[6] who in a double-blind crossover study comparing timolol and carteolol found reductions of 10% and 13% after two and four weeks on carteolol 2% (mean pretreatment intraocular pressure (±SE) was 23·25 (±0·67) mmHg).

There are three previous publications in which the effects of topical carteolol and placebo on intraocular pressure are compared, though these are all single-dose studies.

Gregory and Martin[1] examined the effect of carteolol on intraocular pressure in six normal volunteers. Carteolol was administered as a drop of 2% solution and as an oral dose of 20 mg. The differences in the effects of placebo and topical carteolol on intraocular pressure did not reach significance (maximum difference in effect (placebo-carteolol)=2·8 mmHg; df=10, $t=-1\cdot275$, $p=0\cdot231$).*

Kitazawa *et al.*[2] studied the ocular hypotensive effect of topical carteolol in subjects with raised intraocular pressure. The peak effect of carteolol 1% and 2% occurred at 2 hours; significant reductions in intraocular pressure were obtained from two to three hours with carteolol 1%, and from zero to six hours with carteolol 2%. There was a 10% reduction in intraocular pressure six hours after the administration of carteolol 2%, which is in agreement with the result of our multidose study.

We are unable to comment on the 12-hour control of intraocular pressure, because we measured intraocular pressures six to eight hours after dosage. Nevertheless, when comparing carteolol 2% with placebo, neither Kitazawa *et al.*[2] nor Negishi *et al.*[3] obtained significant reductions in intraocular pressure at eight hours, which raises some doubt about the suitability of a twice daily regimen when using carteolol to treat raised intraocular pressure.

We are grateful to Dr R G Newcombe, of the Department of Medical Computing and Statistics, University of Wales College of Medicine, for his help and advice in the analysis of this study.

References

1 Gregory J, Martin BK. Ocular effects and pharmacokinetics of carteolol in volunteers. *Invest Ophthalmol Vis Sci* 1986; **27** (suppl): 349.

2 Kitazawa Y, Azuma I, Takase M, Komemushi S. Ocular hypotensive effects of carteolol hydrochloride in primary open angle glaucoma and ocular hypertensive patients. *Nippon Ganka Gakkai Zasspi* 1981; **85**: 798–804.

3 Negishi C, Ueda S, Kanai A, *et al.* Effect of beta-blocking agent, carteolol, on healthy volunteers and glaucoma patients. *Nippon Ganka Gakkai Zasshi* 1982; **85**: 57–66.

4 Armaly MF. Selective perimetry for glaucomatous defects in ocular hypertension. *Arch Ophthalmol* 1972; **87**: 518–24.

5 Hills M, Armitage P. The two period cross-over clinical trial. *Br J Clin Pharmacol* 1979; **8**: 7–20.

6 Horie T, Takahashi O, Shirato S, Kitazawa Y. Comparison of ocular hypotensive effects of carteolol eye drops and timolol eye drops. *Jpn J Clin Ophthalmol* 1982; **36**: 1065–70.

Accepted for publication 27 November 1986.

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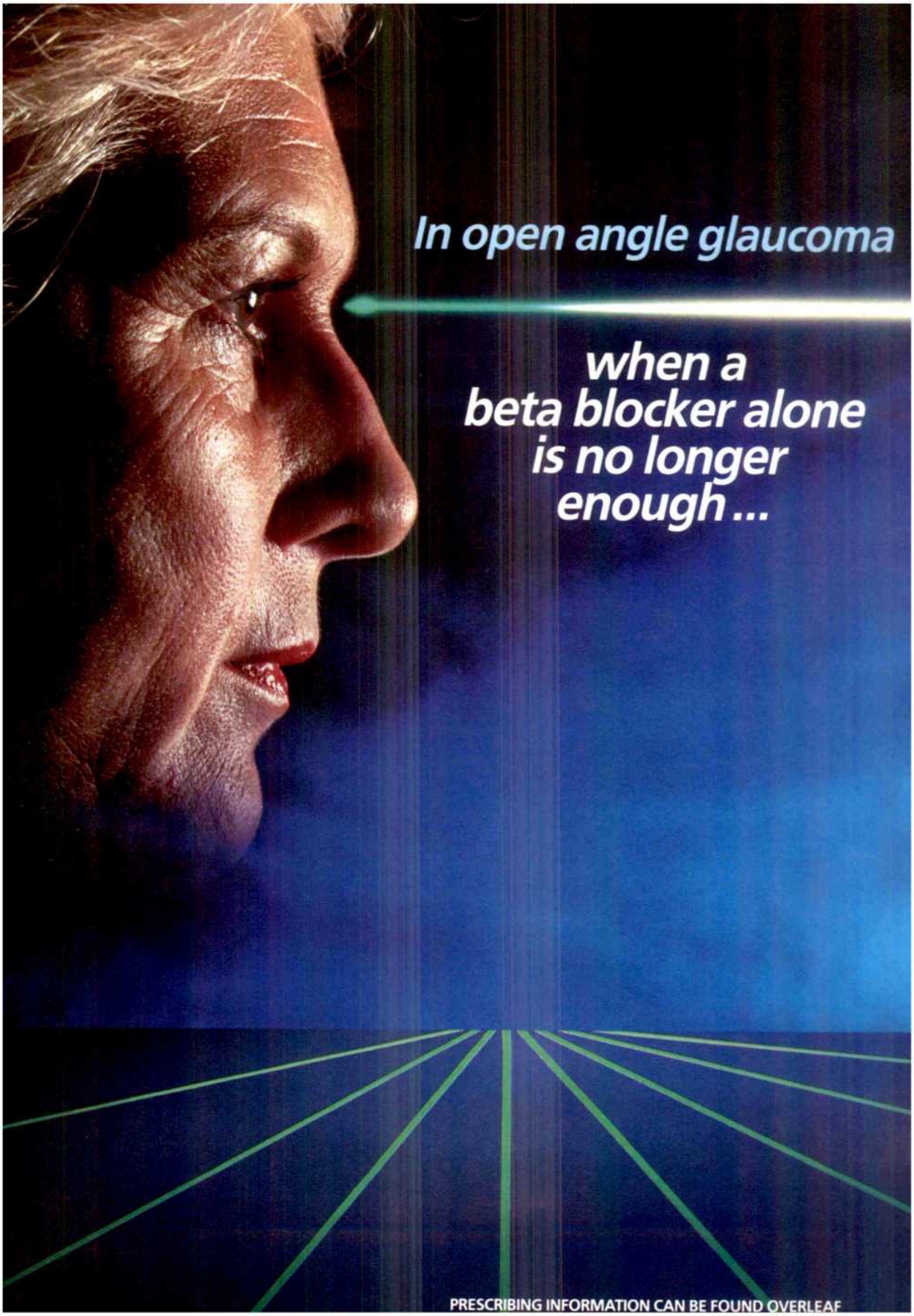
*Calculations based on data supplied by manufacturer.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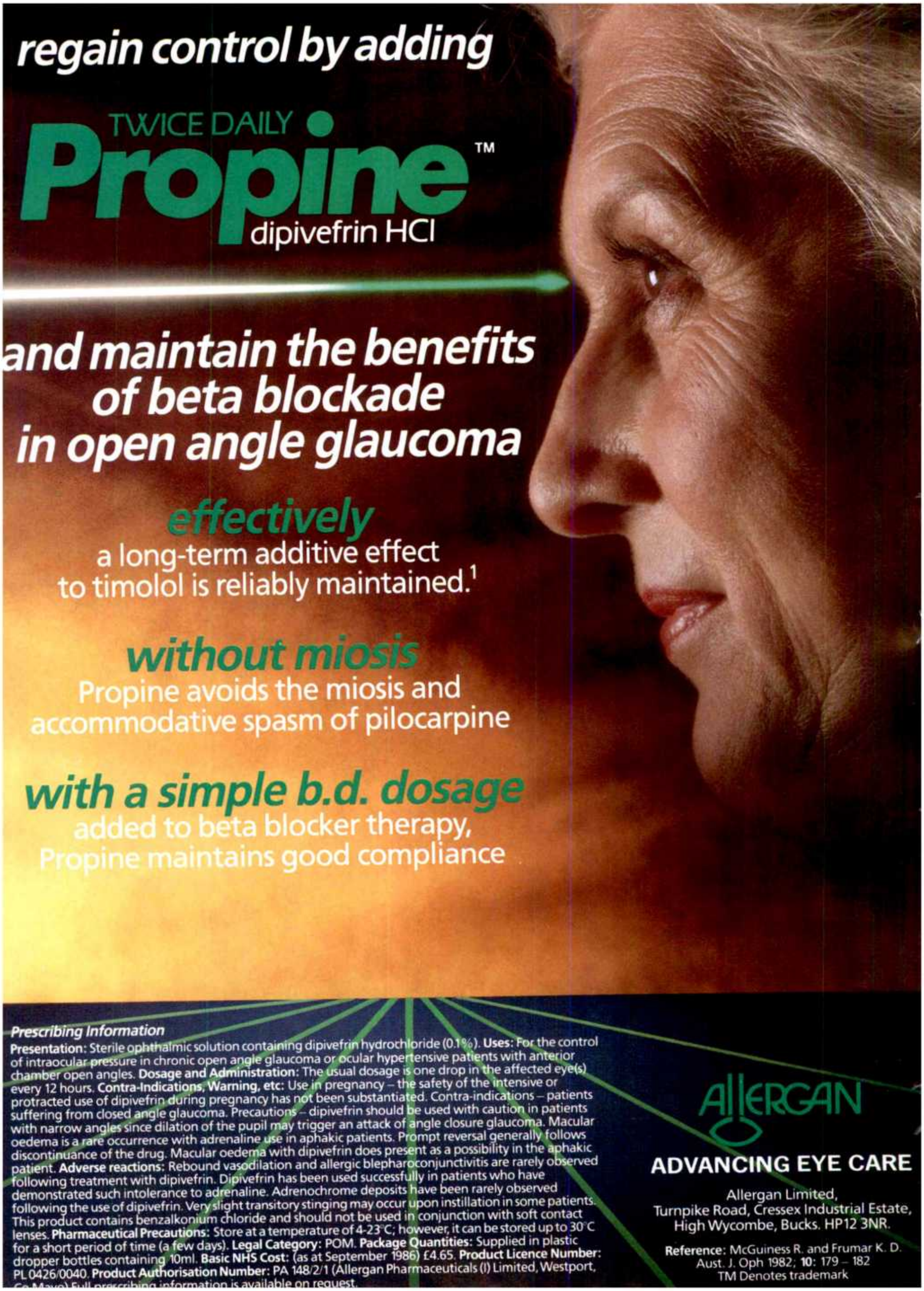

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British Journal of Ophthalmology, 1988, **72**, 29–35

Tissue response to aqueous drainage in a functioning Molteno implant

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SUMMARY The tissue reaction to a functioning Molteno implant has been studied by light microscopy and by scanning and transmission electron microscopy. The material was obtained from an aphakic 83-year-old human eye which required enucleation because of intractable bullous keratopathy, despite well controlled intraocular pressure. The tissue response around the silicone rubber tube was that of simple fibroblastic activity. Around the implant, however, there was fibrous tissue in which necrotic cell debris was prominent. No significant inflammation was observed in this tissue, but the choroid beneath the implant showed a focal inflammatory cell infiltrate. The morphology suggests that the tissue around all surfaces of the implant (450 mm^2) is exposed to aqueous, which seems to have a toxic effect on the encapsulating connective tissue. The changes seen in the tissue exposed to draining aqueous are similar to those described in experimental studies of the effect of aqueous on cell growth in tissue culture.

Various surgical drainage procedures using the implantation of foreign material have been developed in the treatment of glaucoma. In 1960 Ellis[1] reviewed the history of attempts to provide a suitable drainage fistula, and the material used to maintain a channel out of the eye includes horsehair, which was glued to the cheek over silk, various metals, gelatin, cartilage setons, and finally plastic materials. In recent years plastic materials have been modified and improved to obtain encouraging results even in previously unfavourable cases.[2-5]

In 1969 Molteno[6 7] introduced a new plastic implant for the management of neovascular glaucoma, and after several modifications[8 9] it has been accepted as a useful tool for severe cases of uncontrolled intraocular pressure.[9-13]

To our knowledge no histological description on human material has yet been available for the study of the drainage area and the effect of aqueous on the tissue surrounding a functioning Molteno implant. In the case reported here we document the histopathological findings in an eye with a successful Molteno long tube implant.

Case report

A 74-year-old woman developed severe acute angle closure glaucoma in both eyes in 1975 which was successfully treated by peripheral iridectomies. Thereafter the intraocular pressure remained between 16 and 20 mmHg without supplementary therapy. In 1979 intracapsular cataract extraction was performed in the right eye. The postoperative course was complicated by a transient rise in intraocular pressure to 60 mmHg, and aphakic bullous keratopathy persisted despite normal intraocular pressure without therapy. The corneal condition became painful, and in 1981 an 8·0 mm diameter penetrating keratoplasty with anterior vitrectomy was performed combined with trabeculectomy at the 8 o'clock meridian. The graft remained clear, allowing visual acuity of 6/18, but the intraocular pressure once again proved difficult to control. Therefore a trabeculectomy together with scleral pillar inclusion was performed at the 6 o'clock meridian two months later.

This operation and subsequent cyclocryotherapy in the upper half of the globe were not successful, and the intraocular pressure continued to vary between 12 and 30 mmHg with gradual failure of vision to

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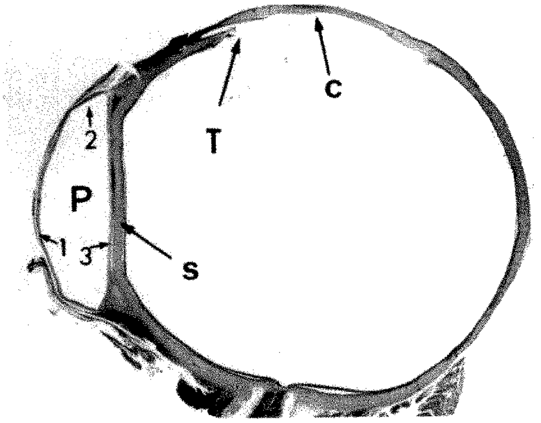

Fig. 1 *Paraffin section of enucleated globe (H and E).* P: *plate cavity with outer wall* (1), *lateral wall* (2), *and inner wall* (3), S: *underlying sclera;* T: *opening of tube tunnel into the globe,* C; *cornea.*

no perception of light in 1983. The corneal graft developed oedema during 1984, and uncontrolled intraocular pressure up to 45 mmHg produced distressing frontal pain.

In June 1985 a single plate Molteno long tube implant was placed on the equatorial sclera under Tenon's fascia in the superonasal quadrant and fixed in position by two 8·0 virgin silk sutures at its anterior edge. The proximal part of the tube was buried under a partial thickness scleral flap and its free end tucked temporarily under the medial rectus muscle. Eight weeks later the conjunctiva was reopened and the free end of the tube was repositioned under a scleral flap contiguous with the previous flap. These flaps therefore formed a continuous intrascleral tunnel for the tube, which was inserted in the eye via a stab incision under the limbal end of the second flap. Postoperative medication consisted of betamethasone drops and chloramphenicol drops four times daily and atropine drops twice daily for one month. The intraocular pressure remained approximately 22 mmHg, and the patient had no further frontal pain.

Eight months later, however, painful bullous keratopathy developed without increase in intraocular pressure, and the eye was enucleated. Immediately after enucleation the globe was fixed in cacodylate-buffered glutaraldehyde (2%).

MACROSCOPIC EXAMINATION

On external examination the plate was located in the superonasal equatorial region of the globe within episcleral tissue. It measured 13 mm in diameter with a calculated total surrounding surface area of approximately 450 mm^2. As the plate was expected to be too hard for sectioning, it was removed from its smooth walled episcleral cavity after cutting it free from the two scleral fixation sutures. The softer drainage tube into the anterior chamber was left in situ. There were no adhesions between the plate material and the surrounding fibrous tissue. The cavity itself formed an oval space (Fig. 1) corresponding to the slit-lamp observation of a deep drainage bleb around the plate. Apart from glaucomatous atrophy the ocular tissues showed no significant abnormality. The eye was then sectioned in an oblique plane to display the pupil, the optic nerve, and the central part of the bleb cavity for paraffin histology.

LIGHT MICROSCOPIC EXAMINATION

Serial sections for light microscopy were stained with haematoxylin-eosin, and additional special stains — periodic acid Schiff (PAS), alcian blue/PAS, PAS after diastase, Prussian blue, reticulin, Masson trichrome, picro-Mallory V, Bodian, Loyez — were performed on selected levels.

Microscopic examination confirmed the features of longstanding bullous keratopathy with formation of vesicles beneath the corneal epithelium and partial loss of Bowman's layer. Peripheral corneal vascularisation was also present. The corneal transplant could be identified by stromal scarring at the host-graft junction with small gaps in Descemet's membrane at this site, allowing the formation of a thin retrocorneal membrane localised to the area of the wound. The inferonasal trabeculectomy was demonstrated histologically as half-thickness sclera lined internally by fibrotic remnants of ciliary body. Elsewhere the angle of the anterior chamber was closed by iridocorneal adhesion, and the residual trabecular meshwork was hyalinised and degenerate.

At the penetration site of the Molteno tube into the anterior chamber there was some distortion of Descemet's membrane and adjacent atrophic iris tissue, but no significant inflammatory reaction was found (Fig. 2a, b). The intrascleral tunnel for the tube was lined by a layer of spindle-shaped cells which extended up to the opening into the plate. The cavity of the Molteno plate was surrounded by a rim of fibrous tissue (Fig. 2c, d), which was distinguished from scleral collagen by its looser architecture and the presence of abundant PAS-positive granules (Fig. 2e, f, g). These granules were not present elsewhere in the episclera of this eye or in a corresponding episcleral area of an eye enucleated for an intraocular melanoma. The inner wall, the lateral wall, and the outer wall of the plate cavity, however, were of identical morphological appearance. Unlike the lining of the tube tunnel there was no cellular

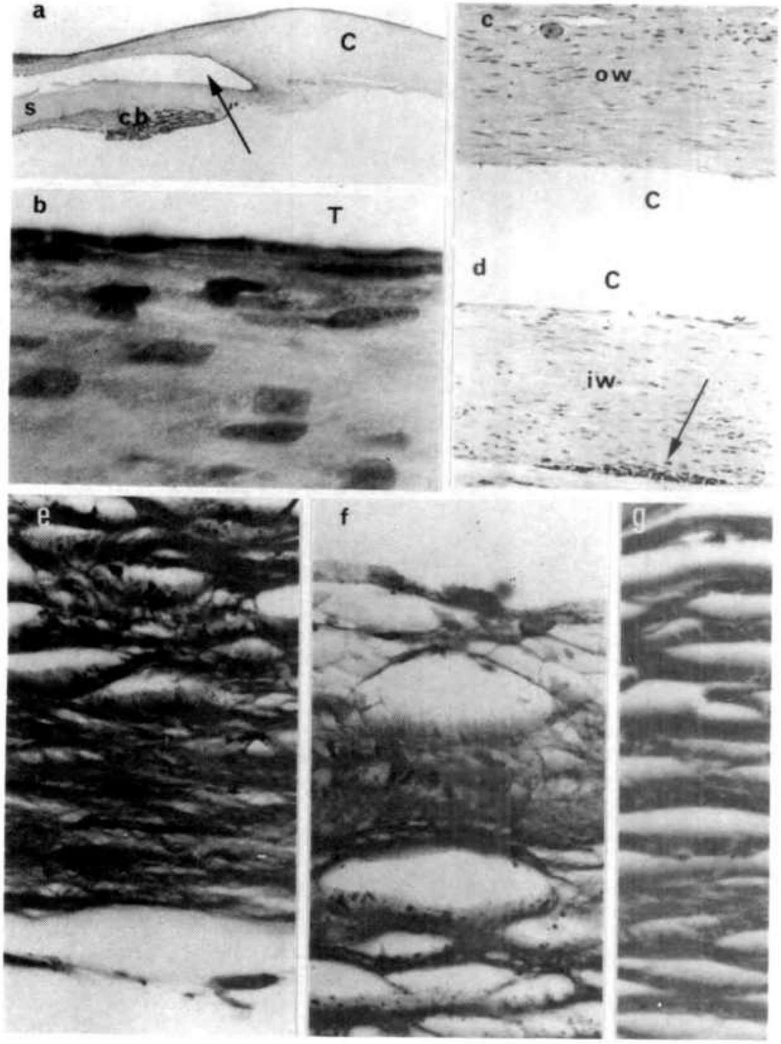

Fig. 2 *Light microscopic appearance of tissues around implant.* (a) *Tube tunnel (arrow) near perforation into anterior chamber (H and E); note angle closure.* C: *Cornea,* cb: *ciliary body,* s: *sclera.* (b) *Detail of spindle cells lining tube tunnel* (T) *(H and E); note absence of inflammatory cells.* (c) *Outer wall* (ow) *of plate cavity* (C) *(H and E); note absence of surface differentiation.* (d) *Inner wall* (iw) *of plate cavity* (C) *(H and E); note absence of surface differentiation and inflammatory cell infiltrate (arrow) at border with intrinsic scleral collagen.* (e) *Detail of outer wall (alcian blue/PAS); compare with tube lining cells in* (b); *note numerous granules between the collagen lamallae.* (f) *Detail of inner wall (alcian blue/PAS); note similar granules as in outer wall.* (g) *Sclera shown for comparison (alcian blue/PAS); note absence of granules and more regular architecture of collagen lamellae.*

surface differentiation in the plate cavity, the latter being simply lined by collagen and fibroblasts (Fig. 2c, d).

Only a few inflammatory cells and macrophages were seen predominantly within the inner wall and some cellular debris was also present. Evidence of abnormal fibroblastic proliferation was not seen. Capillaries were more numerous over the implant than within the episclera elsewhere, but there were no features of oedema, and there was only a very mild focal plasmacytic response around some of these vessels.

Inflammation, in the form of a giant cell granulomatous reaction, was much more prominent around the intrascleral suture material, and a focal inflammatory cell infiltrate was found between the sclera and the inner wall of the plate cavity (Fig. 3a, c). There was also focal inflammation within the choroid beneath the Molteno implant (Fig. 3a), but the remainder of the choroid was normal. The retinal pigment epithelium overlaying this area of focal choroiditis showed an increased number of drusen (Fig. 3b) in comparison with the rest of the eye. The retina showed advanced glaucomatous atrophy with loss of ganglion cells and nerve fibres and a deeply cupped optic disc. A transverse section across the optic nerve revealed marked thickening of the pial septa and almost complete axonal loss.

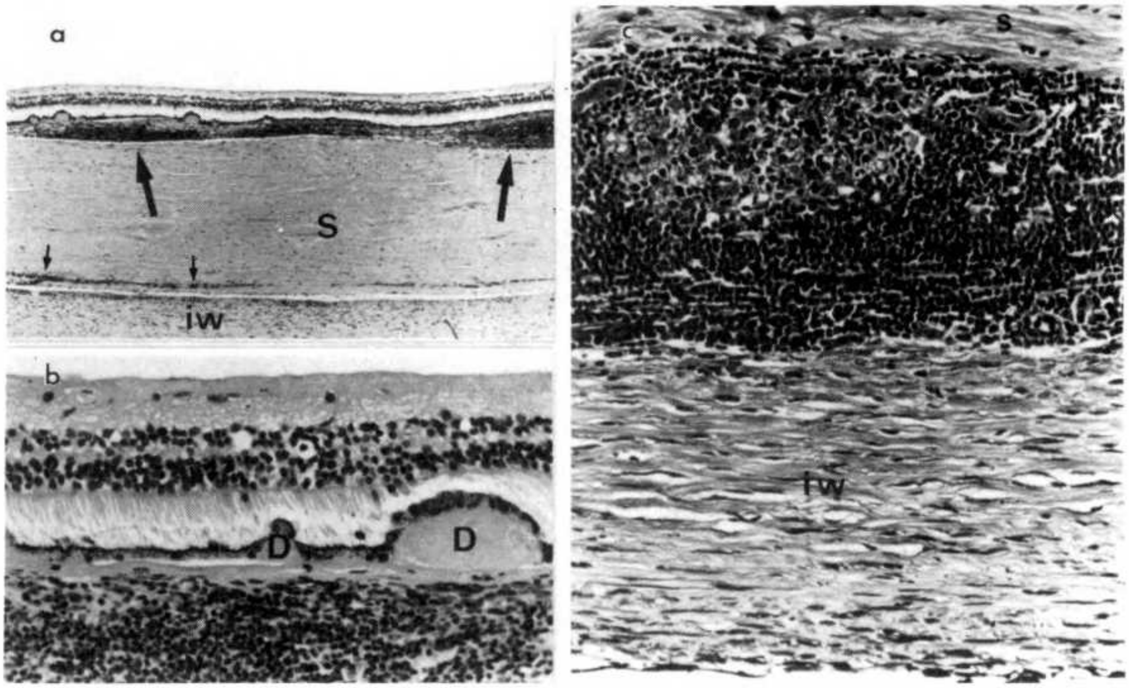

Fig. 3 (a) *Low-power section across coats of the eye beneath plate cavity showing focal inflammatory cell infiltrate in the choroid (arrow) and beneath the inner wall* (iw) of the cavity (H and E); *intervening sclera* (s) *shows no significant abnormality*. (b) *Drusen formation* (D) *of RPE overlying cellular infiltrate in choroid (H and E)*. (c) *Granulomatous inflammatory cell infiltrate between sclera* (s) *and inner wall* (iw) *(H and E)*.

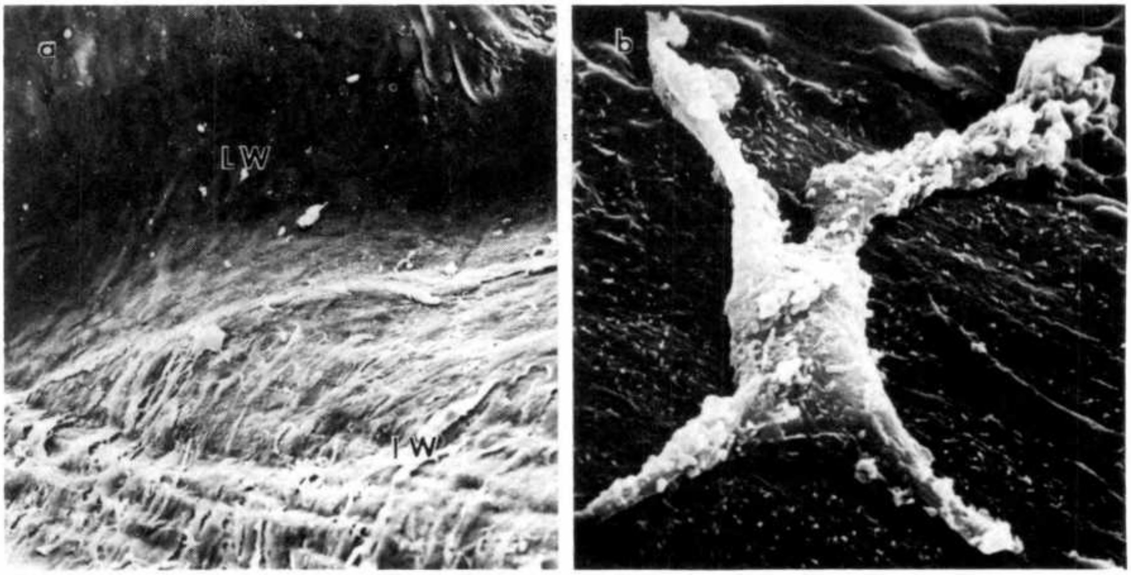

Fig. 4 (a) *Inner wall* (IW) *and lateral wall* (LW) *of plate cavity showing almost complete absence of cell covering. SEM*. (b) *Isolated cell on surface of inner wall of plate cavity. SEM*.

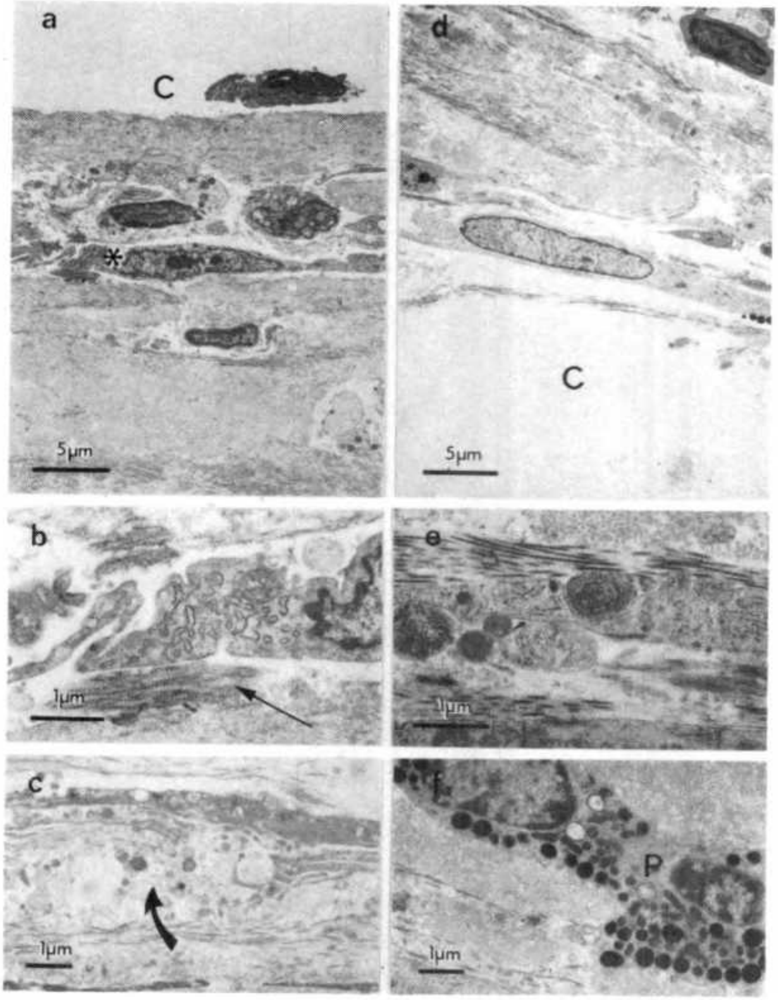

Fig. 5 (a) *Inner wall of plate cavity (TEM).* C: *cavity; note absence of surface differentiation.* *: *fibroblast shown in* (b). (b) *Detail of* (a) *showing active fibroblast and adjacent collagen (arrow) (TEM).* (c) *Cell process of fibroblast (TEM); note numerous extracellular granules (arrow).* (d) *Outer wall of plate cavity (TEM).* C: *cavity; note absence of surface differentiation similar to (a).* (e) *Cell processes and loose collagen bundles in outer wall (TEM).* (f) *One of the few polymorphonuclear leucocytes* (P) *found between collagen fibres in the outer wall.*

ELECTRON MICROSCOPIC INVESTIGATION

Tissue from the roof and the adjacent lateral and inner wall of the plate cavity was taken from the calottes and processed routinely for scanning electron microscopy (SEM). Several blocks from the same area were also processed in a conventional fashion for transmission electron microscopy (TEM) and embedded in Araldite. Ultrathin sections were cut with an LKB Ultrotome III, stained with uranyl acetate and lead citrate, and examined with a Philips 301 transmission electron microscope. Material from the tube tunnel was not studied by electron microscopy to preserve the entirety of the specimen for light microscopic sections.

Ultrastructural examination of the connective tissue around the plate cavity revealed similar features in both the outer and inner wall. By SEM the outer and lateral wall appeared slightly smoother than the inner wall but no significant difference could be noted (Fig. 4a). A few large cells were present on each side facing the plate but there was no continuous cellular layer lining the cavity (Fig. 4b). TEM showed the wall to be composed mainly of collagen which was of normal appearance but not as regularly arranged as in the sclera (Figs. 5 and 6). Some fibroblasts showed features of activation such as a prominent rough endoplasmic reticulum and a dilated Golgi apparatus (Fig. 5b). Inflammatory cells, for example, polymorphonuclear leucocytes, were seen only occasionally (Fig. 5f). There was, however, evidence of cell death, and extracellular granules and other cellular debris were found between the collagen

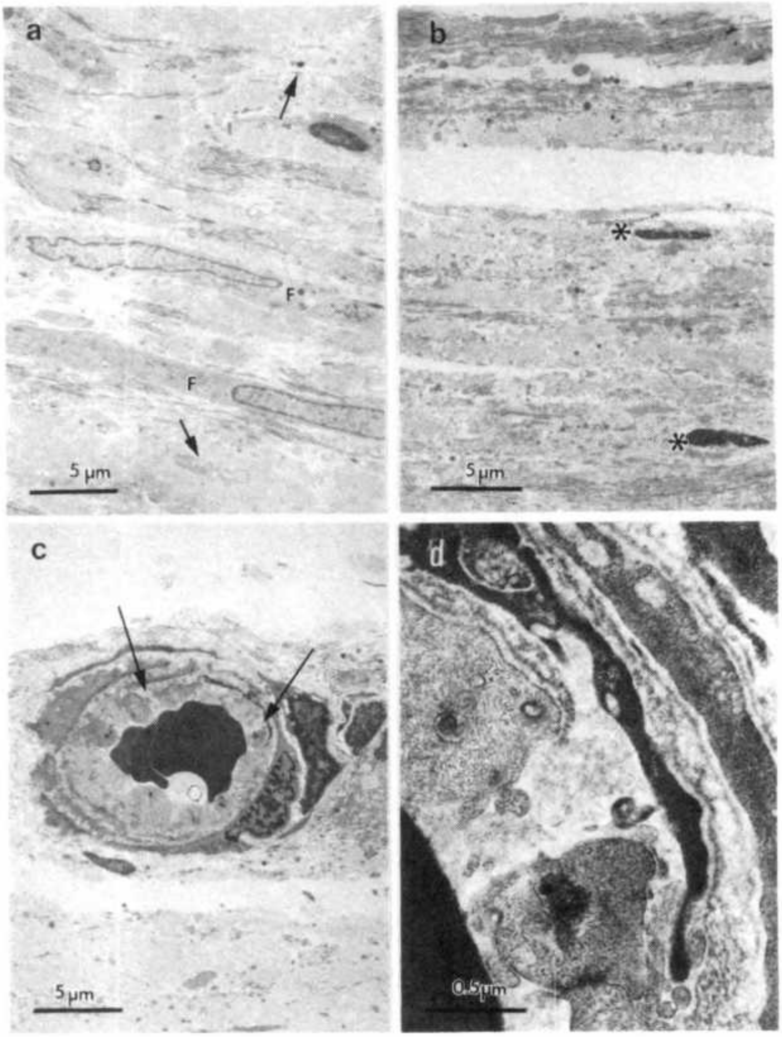

Fig. 6 (a)*Inner wall of plate cavity showing irregular collagen arrangement and some cellular debris (arrow) but also well preserved fibroblasts* (f). *TEM.* (b) *Outer wall of plate cavity where cell death (*) and cellular debris are more prominent (TEM); note loose architecture of collagen.* (c) *Episcleral vessel at outer aspect of outer wall showing gaps (arrow) between endothelial cells. TEM.* (d) *Higher magnification of an intercellular gap. TEM.*

lamellae (Fig. 6a, b). As observed by SEM there was no continuous cell layer lining the inner aspects of either outer or inner wall: the surface was formed predominantly by collagen fibres and only sparsely interspersed cells. Episcleral vessels over the implant showed prominent intercellular gaps within the endothelium. (Fig, 6c, d).

Discussion

The two major problems of this type of glaucoma surgery are uncontrolled hypotonia and late obstruction of the drainage fistula by excessive scarring due to fibrovascular proliferation.

The Molteno long tube implant in this case was inserted in a two-stage procedure as recommended by Molteno[9] to avoid an undesired rapid fall in intraocular pressure. In subsequent cases we have devised a modification which allows a satisfactory one-stage operation. The location of the plate and insertion of the tube is now carried out as a single operation using an absorbable ligature of 8·0 gauge polyglycolic acid suture to provide temporary restriction of aqueous drainage along the tube. This seems to allow adequate initial drainage without hypotonia.

To avoid fibroblastic proliferation with subsequent occlusion of the drainage bleb, Molteno has recommended a more posterior location of the plate and additional heavy antifibrosis and immunosuppressive therapy.[8] This medication can show significant side effects,[10 12] and we have not used such a regimen. It appears therefore of great interest that, despite the absence of such drugs in the present case, the bleb wall did not appear abnormally inflamed or thickened.

Aqueous has been reported to inhibit the initiation of growth of fibroblasts.[14-16] This might explain the features of degeneration and cell death seen in the tissue around the implant. It would also support the concept that antifibrosis therapy is not necessarily needed to prevent undesired scarring of the bleb, although in some individuals aqueous may not show this inhibitory effect on fibroblasts.[15] The apparent difference between the lining of the tube tunnel and the fibrous tissue around the plate cavity might partly be due to the constituent materials in the implant (silicone rubber tube and polyacrylate), but the main reasons for the recognisable morphological differences is consistent with the effect of aqueous on fibroblasts observed in tissue culture.[14]

The focal choroiditis localised to the area beneath the implant plate may be another indication of the toxicity of aqueous under unphysiological conditions. This focal uveal inflammation might be mediated by products of the dying cells observed in the reactive fibrous tissue of the inner wall or perhaps by the aqueous itself reaching the choroid by diffusion across the sclera. The sclera, however, appeared unremarkable (Fig. 2g).

The Molteno implant is designed to utilise the outer wall of the plate cavity for the absorption of aqueous, but from our histological and electron microscopical findings it is evident that the lateral and the inner wall of the implant are equally involved. Indeed, no marked difference could be found either in collagen composition or cellular involvement in the tissue on either side of the plate, which lay loosely in its cavity. This indicates that the drainage area is much larger than the single surface previously described.[9] The true surface area available for aqueous drainage extends on all surfaces of the plate. We therefore consider that for comparison with the absorptive area of other drainage devices the Molteno single plate should be attributed an area of 450 mm^2. The presence of numerous episcleral vessels at the site of the implant points to a vascular component in the tissue reaction, since the equatorial episclera is relatively avascular under normal circumstances.[17] The prominent gaps between the endothelial cells may indicate an increase in fluid exchange perhaps related to the direct biological effect of aqueous humour.

Further studies are required to investigate the effects of aqueous on the newly formed fibrous tissue and to elucidate its pathway into the vascular system, as this seems important in the maintenance of drainage in fistulising operations.

We thank Professor W R Lee for his valuable advice and encouragement and Mrs D Aitken for the electron microscopy.

References

1 Ellis R. Reduction of intraocular pressure using plastics in surgery. *Am J Ophthalmol* 1960; **50**: 733–43.
2 Egerer I. Klinische Erfahrungen bei fistulierenden Glaukomoperationen mit Silikonkathetern. *Klin Monatsbl Augenheilkd* 1979; **174**: 434–41.
3 Schocket SS, Lakhanpal V, Richards RD. Anterior chamber tube shunt to an encircling band in the treatment of neovascular glaucoma. *Ophthalmology* 1982; **89**: 1188–94.
4 Kuljava Z, Ljubojeviv V, Momirov D. Draining implant for neovascular glaucoma. *Am J Ophthalmol* 1983; **96**: 372–6.
5 Krupin T, Kaufman P, Mandell AI, *et al*. Long-term results of valve implants in filtering surgery for eyes with neovascular glaucoma. *Am J Ophthalmol* 1983; **95**: 775–82.
6 Molteno ACB. New implant for drainage in glaucoma. Animal trial. *Br J Ophthalmol* 1969; **53**: 161–8.
7 Molteno ACB. New implant for drainage in glaucoma. Clinical trial. *Br J Ophthalmol* 1969; **53**: 606–15.
8 Molteno ACB, Van Rooyen MMB, Bartholomew RS. Implants for draining neovascular glaucoma. *Br J Ophthalmol* 1977; **71**: 120–5.
9 Ancker E, Molteno ACB. Die chirurgische Behandlung des chronischen Aphakieglaukoms mit dem Moltenokunststoffimplantat. *Klin Monatsbl Augenheilkd* 1980; **177**: 365–70.
10 Brown RD, Cairns JE. Experience with the Molteno long tube implant. *Trans Ophthalmol Soc UK* 1983; **103**: 297–311.
11 Ancker E, Molteno ACB. Molteno drainage implant for neovascular glaucoma. *Trans Ophthalmol Soc UK* 1982; **102**: 122–4.
12 Cairns JE. The Molteno long-tube implant. *Trans Ophthalmol Soc UK* 1983; **103**: 39–41.
13 Molteno ACB, Ancker E, Van Biljon G. Surgical technique for advanced juvenile glaucoma. *Arch Ophthalmol* 1984; **102**: 51–7.
14 Kornblueth W, Tenenbaum E. The inhibitory effect of aqueous humor on the growth of cells in tissue cultures. *Am J Ophthalmol* 1956; **42**: 70–4.
15 Herschler T, Claflin A, Fiorentino G. The effect of aqueous humor on the growth of subconjunctival fibroblasts in tissue culture and its implications for glaucoma surgery. *Am J Ophthalmol* 1980; **89**: 245–9.
16 Radius RL, Herschler T, Claflin A, Fiorentino G. Aqueous humor changes after experimental filtering surgery. *Am J Ophthalmol* 1980; **85**: 250–4.
17 Hogan MJ, Alvarado JA, Weddell JE. *Histology of the human eye. An atlas and textbook*. Philadelphia, London, Toronto: Saunders, 1971: 192–3.

Accepted for publication 4 December 1986.

British Journal of Ophthalmology, 1988, 72, 36–40

Epithelial cyst in the anterior chamber after penetrating keratoplasty: a rare complication

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SUMMARY We report the case of a 25-year-old man who had a penetrating keratoplasty for keratoconus. A year and a half after surgery a cyst was noted in the anterior chamber, which was observed to enlarge over six months. Because of anxiety about endothelial touch, it was removed surgically. Histologically the cyst was composed of stratified, non-keratinised squamous epithelium attached to loose fibrovascular tissue including islands of melanin-containing epithelial cells. This was interpreted as an epithelial implantation cyst of the anterior chamber of corneal origin attached to iris tissue.

Penetrating keratoplasty is widely used in modern ophthalmic surgery for the visual rehabilitation of patients with corneal scarring or optical aberrations untreatable by other means. Unfortunately the aim of restoring long-term useful vision is not always attained. This may be because of graft rejection, recurrence of disease, optical problems, or complications of surgery.

Surgical complications are relatively rare. We report here a case of anterior chamber epithelial cyst formation after penetrating keratoplasty. Although previously described after cataract surgery, so far as we are aware this is the first reported case occurring after penetrating keratoplasty. Moreover, as the specimen was immediately fixed for electron microscopy, some interesting ultrastructural features are described.

Case report

A 21-year-old male unemployed motor mechanic was first seen in September 1981 having been referred for assessment following an acute corneal hydrops. He had a past medical history of asthma and eczema.

Examination revealed best visual acuities of 6/36−1 in the right eye and 6/60 in the left eye. The right cornea showed a resolving hydrops, and the left swelling with folds in Descemet's membrane and a Fleischer ring. The eyes were normotensive and comfortable. Skin tests revealed marked hypersensitivity to feathers, dog, timothy grass, fescue, tree pollen, wheat grain, and meadow grass. Serum IgE levels were 800 units/ml on a first sample, and 1000 units/ml on a retest.

A right penetrating keratoplasty with unmatched female donor material was performed. The operation went normally, and the patient recovered well, achieving a right visual acuity of 6/18 uncorrected and 6/6 with a contact lens.

Eight months after surgery he sustained a rejection episode with stromal oedema of the whole of the donor tissue and an endothelial rejection line. This required inpatient treatment with hourly 0·1% dexamethasone drops. After this his cornea improved but with some persisting stromal thickening in the lower third of the donor button. The best right visual acuity was 6/9.

Twenty-one months after keratoplasty a cyst was first noted on the anterior surface of the iris in its mid-periphery, in the inferotemporal quadrant of the right eye (Fig. 1). Over the next six months this was observed to enlarge until it threatened to touch the endothelium and to cross the visual axis. The cyst was approximately 8×5 mm (Fig. 2). Visual acuity was reduced to 6/18 and the eye was inflamed, with an intraocular pressure of 35 mmHg.

In view of these findings it was decided to remove the cyst surgically. Under general anaesthesia the right eye was opened by an inferotemporal ab externo approach. The cyst was drained, and found to contain a clear yellow fluid. The collapsed cyst was dissected free of the peripheral cornea and removed

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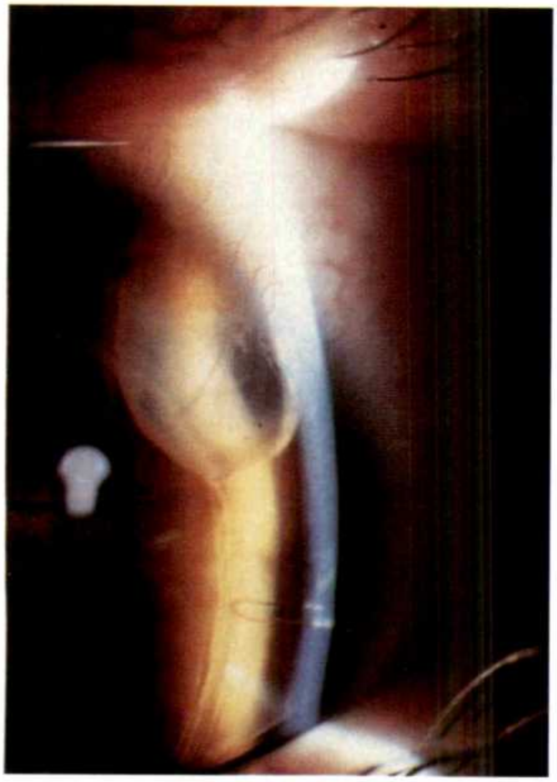

Fig. 1 *Epithelial cyst of right eye 21 months after penetrating keratoplasty.*

from the eye; the tissue was immediately fixed in glutaraldehyde for electron microscopy. A broad iridectomy with reconstruction of the pupil was

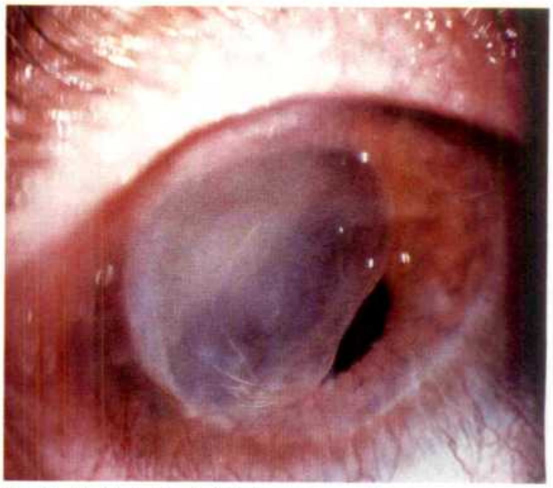

Fig. 2 *Epithelial cyst of right eye immediately prior to removal.*

performed. The wound was closed with interrupted 10/0 nylon sutures. The patient recovered well from the operation and regained a best right visual acuity of 6/12. A year later the corneal endothelium was examined by the Pocklington specular microscope. The endothelial cells were fairly regular in shape and size, the cell count in the central cornea was 1100/mm^2, and there was no evidence of any adherent epithelial cells (Fig. 3).

PATHOLOGICAL EXAMINATION

Following fixation in 2·5% glutaraldehyde in 0·1 molar cacodylate buffer with 3 millimolar calcium, pH7·2, the tissue was postfixed in 1% osmium

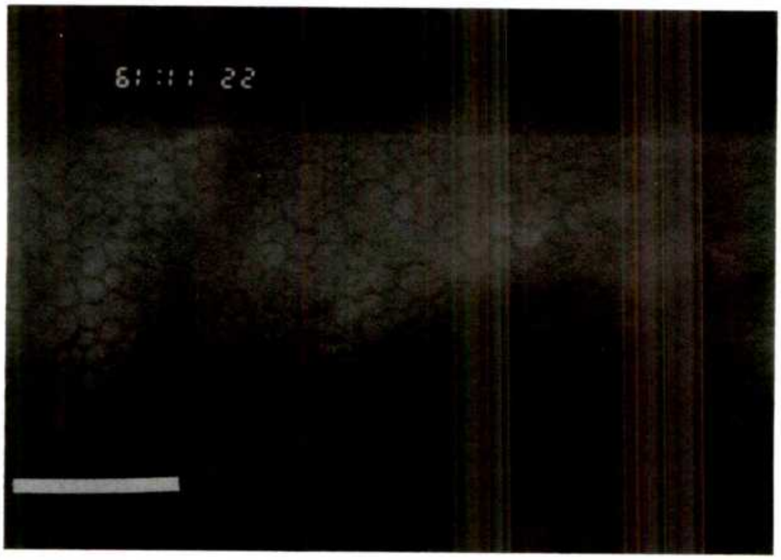

Fig. 3 *A specular micrograph of the patient's corneal endothelium one year after removal of the cyst. The cell count is 1100 cells/mm^2. Most cells are hexagonal in shape, but there is some variation in cell size. Bar=200 µm.*

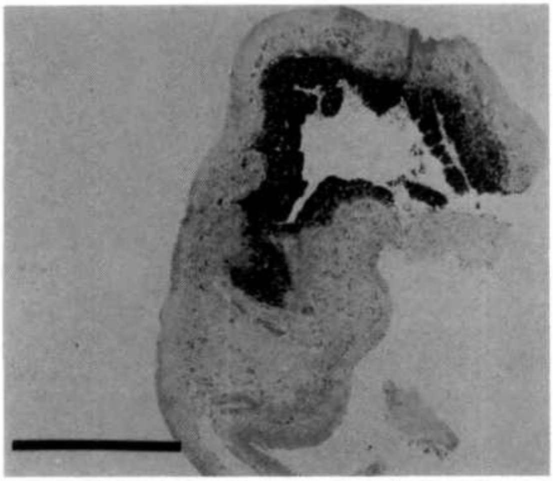

Fig. 4 *A light micrograph of a 1 µm thick plastic section through a portion of the anterior chamber cyst stained with toluidine blue. Pigmented cells resembling iris epithelium are seen towards the top of the picture. Below is an area of fibrovascular tissue. The surface layer is composed of stratified squamous epithelium. Bar=500 µm.*

tetroxide, dehydrated, and embedded in durcapam epoxy resin (Fluorochtome). Sections 2 µm and 5 µm thick were cut and stained with haematoxylin/eosin or toluidine blue for light microscopy. Ultrathin sections were cut, mounted on to copper mesh grids, and stained with uranyl acetate followed by Reynold's lead citrate. The sections were then examined using a Philips 201 transmission electron microscope.

By light microscopy two distinct portions of the cyst were discernible. One was composed of loose fibrovascular tissue with islands of pigmented, non-keratinising, stratified squamous epithelium apparently containing melanin (Fig. 4). These cells resembled the iris pigment epithelium. Scattered mast cells, macrophages, and a few lymphocytes were noted. The remainder of the tissue consisted of a well organised stratified non-keratinising squamous epithelium surrounding a cystic space, and abutting on to loose connective tissue (Fig. 5A). The epithelium resembled normal corneal epithelium, and in most areas was limited to five or six layers (Fig. 5B). There was no histological evidence of malignancy. The 5µm sections were examined for the presence of Barr bodies; none were noted.

Electron microscopy confirmed that the epithelium resembled the epithelium of the cornea with polygonal cells and central nuclei. However, the nuclei were frequently irregular in shape with pale staining chromatin (Fig. 6). An abundance of tonofilaments was seen in many cells (Figs. 6, 7). A prominent feature, not normally associated with corneal or conjunctival epithelium was the abundance of desmosomes in close association with clusters of tonofilaments (Fig. 7), which at lower power resembled junctional complexes (Fig. 6).

Discussion

This case appears to be of an iatrogenic epithelial cyst of the anterior chamber following penetrating keratoplasty for corneal hydrops. A rare complication of ocular surgery is the growth of corneal epithelium in the anterior chamber. This may either invade the anterior chamber (usually through a poorly apposed wound) or, if implanted at the time of surgery, form a cyst in the anterior chamber.

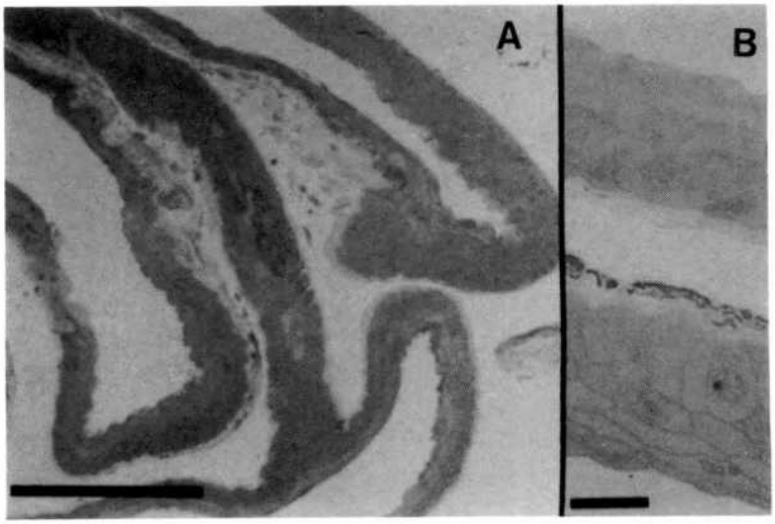

Fig. 5A *A light micrograph of a 1 µm thick plastic section through the remainder of the cyst stained with toluidine blue. The cyst is composed of well organised stratified non-keratinising epithelium with some loose connective tissue. Bar=200 µm.*
5B *A higher power light micrograph demonstrating the five or six layers of epithelial cells. Bar=20 µm.*

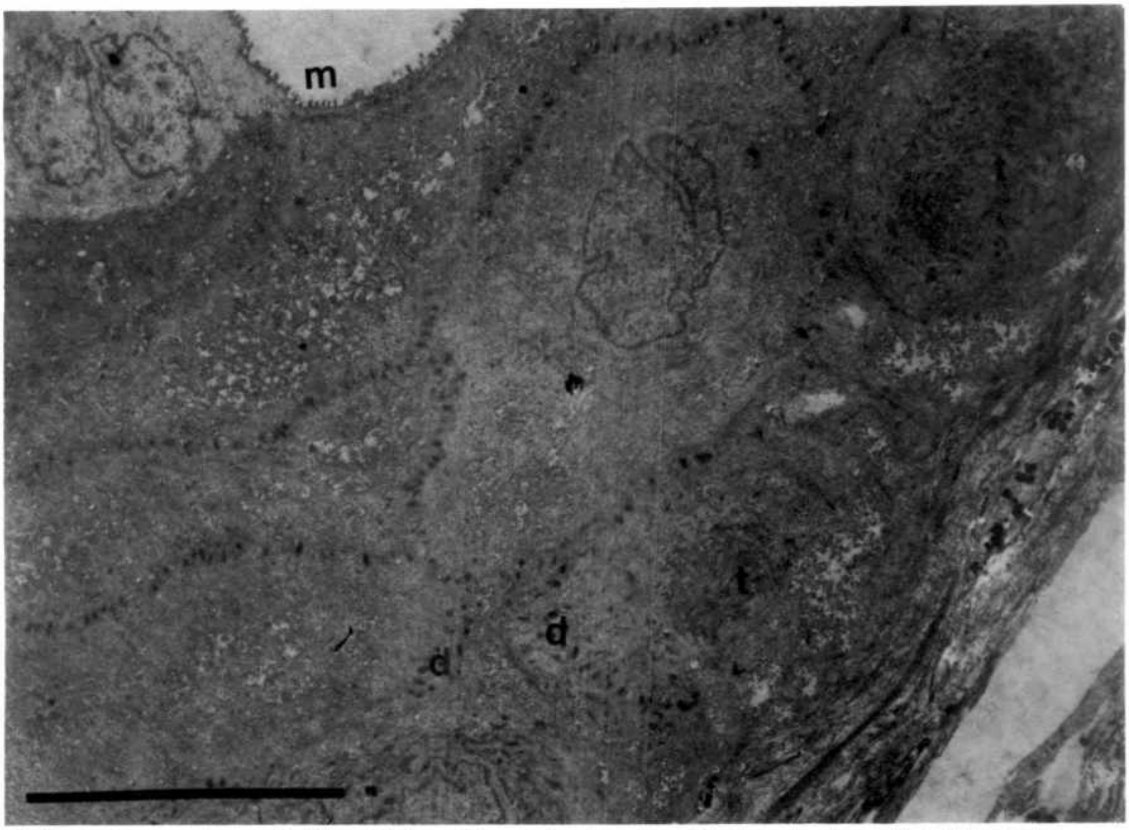

Fig. 6 *An electron micrograph of the epithelium of the cyst showing microvilli* (m), *an abundance of tonofilaments* (t). *Accumulations of desmosomes* (d) *can be seen in some cells. Bar=10 µm.*

Although anterior chamber epithelialisation has been described after penetrating keratoplasty,[1-3] we are unaware of any previous descriptions of epithelial cysts after this operation. The clinical appearance and behaviour of the lesion in this patient were unlike what has been reported for anterior chamber epithelialisation.

The cyst could be derived from either host or donor epithelium. Our finding that Barr bodies were not seen suggests that the original cells were of host origin, but is not conclusive. If they were, we presume that the original germinal cells may have been carried to the anterior chamber at the time of host cornea trephination. It would seem unlikely that poor wound apposition was the source of epithelial cell invasion as has been suggested for postcataract extraction anterior chamber epithelialisation,[4] since, as Sugar *et al.*[5] have pointed out, such a resulting fistula would be readily detectable and would have been repaired without delay. Furthermore, previous reports of anterior chamber epithelialisation have given a mean time from keratoplasty to diagnosis of less than four months[6] compared with the 21 months which elapsed before any abnormality was detected in the patient reported on here.

The relationship of the cyst to the rejection episode must remain hypothetical. However, a number of interactions are theoretically possible. Microscopic growth of the cyst with early vascularisation might have sensitised the host to the allograft if the epithelium were derived from the donor. The rejection episode itself, with the resultant inflammation and presence of biologically active substances such as lymphkines, might have broken a state of dormancy which had existed since the initial penetrating keratoplasty, and which might in part have been mediated immunologically irrespective of whether the tissue was of host or donor origin. The treatment of the rejection with high doses of steroid might have provided suitable conditions in the anterior chamber for growth of the cyst to begin. Finally, it could be supposed that, had the cyst been of donor origin, the cells would have been killed by immunological mechanisms during the rejection episode.

Histologically the presence of mast cells is of

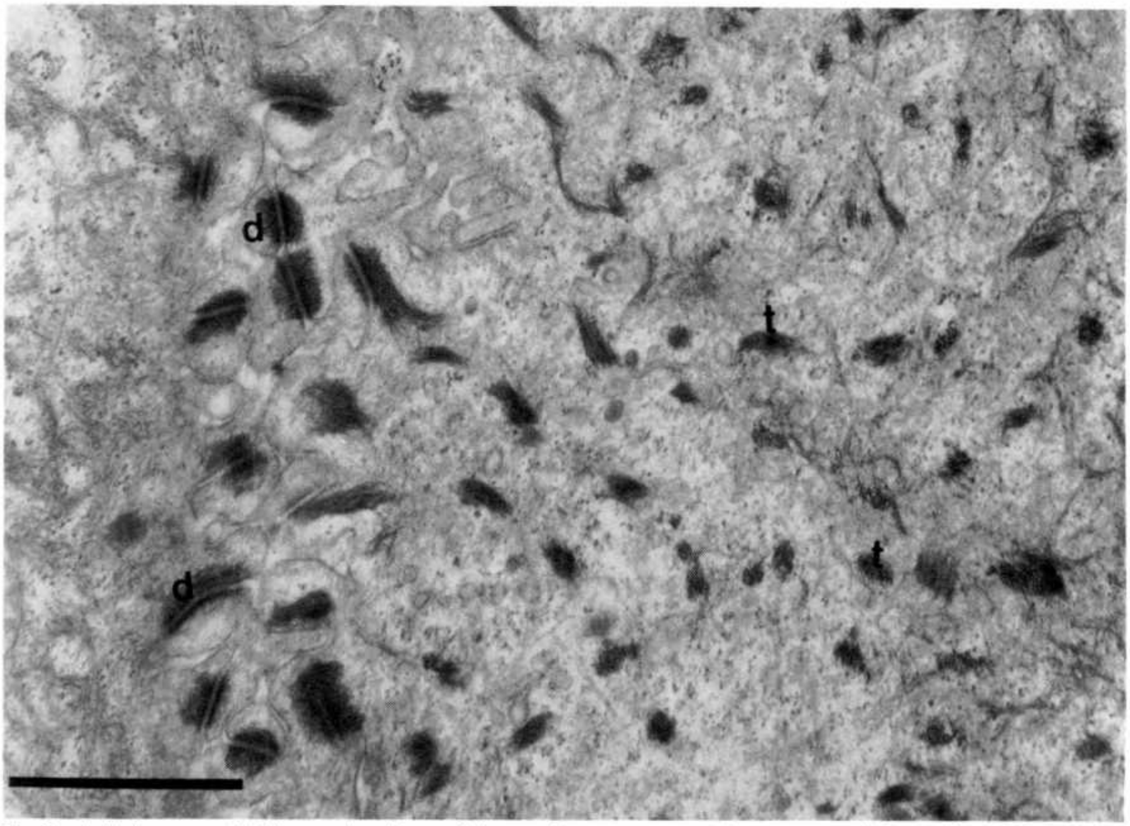

Fig. 7 *At higher power, highly convoluted intercellular membranes are seen, with numerous well-formed desmosomes* (d). *An abundance of short length tonofilaments* (t) *not associated with a cell membrane are also present. Bar=1 µm.*

interest. These may have been involved in the elaboration of prostaglandins which in turn were responsible for the elevation of intraocular pressure noted prior to removal of the cyst. Although desmosome complexes are seen in fetal corneal epithelium, they are not typical of the adult tissue. Whether they represent a return to the embryonic state in the environment of the anterior chamber or a response to drug therapy of some unknown variable is not known.

The clinical behaviour of this anterior chamber epithelial cyst mirrors that seen after cataract surgery in that the prognosis for vision appears good. The good prognosis is further enhanced by the endothelial cell count remaining reasonably high despite the rejection episode and the additional surgery. This contrasts markedly with the prognosis for anterior chamber epithelisation.[5]

Dr Claoué is a Wellcome Trust Research Fellow. Dr Lewkowicz-Moss is funded by the Sir Halley Stewart Trust. We thank Dr T H Moss, for help in interpreting the pathological specimens, and Mr K Gross for doing the specular microscopy.

References

1 Mazow ML, Stephens RW. An unusual complication after keratoplasty. *Surv Ophthalmol* 1966; **11:** 205–8.
2 Leibowitz HM, Elliott JH, Boruchoff A. Epithelialization of the anterior chamber following penetrating keratoplasty. *Arch Ophthalmol* 1967; **78:** 613–7.
3 Kurz GH, D'Amico RA. Histopathology of corneal graft failures. *Am J Ophthalmol* 1968; **66:** 184–99.
4 Maumenee AE, Paton D, Morse PH. Review of 40 histologically proven cases of epithelial downgrowth following cataract extraction and suggested surgical management. *Am J Ophthalmol* 1970; **69:** 598–603.
5 Sugar A, Meyer RF, Hood I. Epithelial downgrowth following penetrating keratoplasty in the aphake. *Arch Ophthalmol* 1977; **95:** 464–7.

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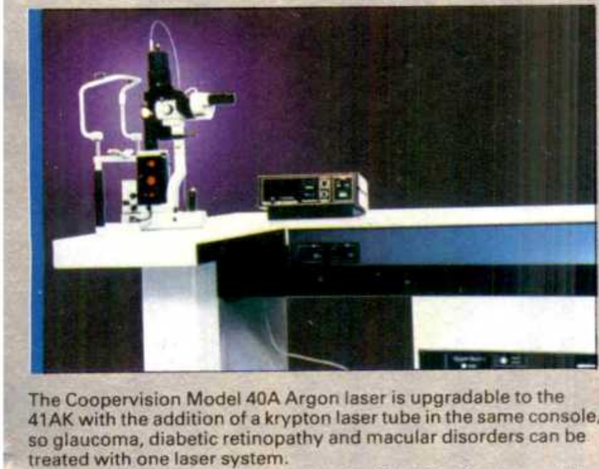

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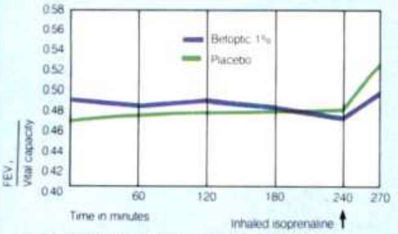

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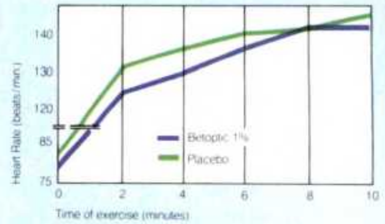

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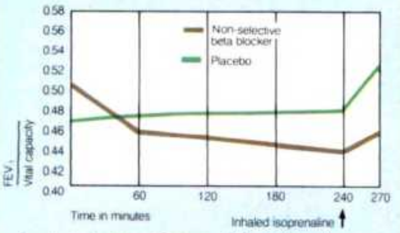

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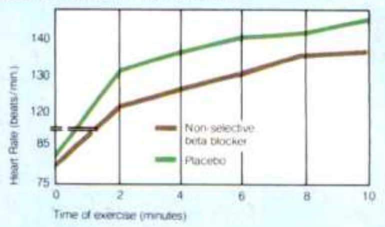

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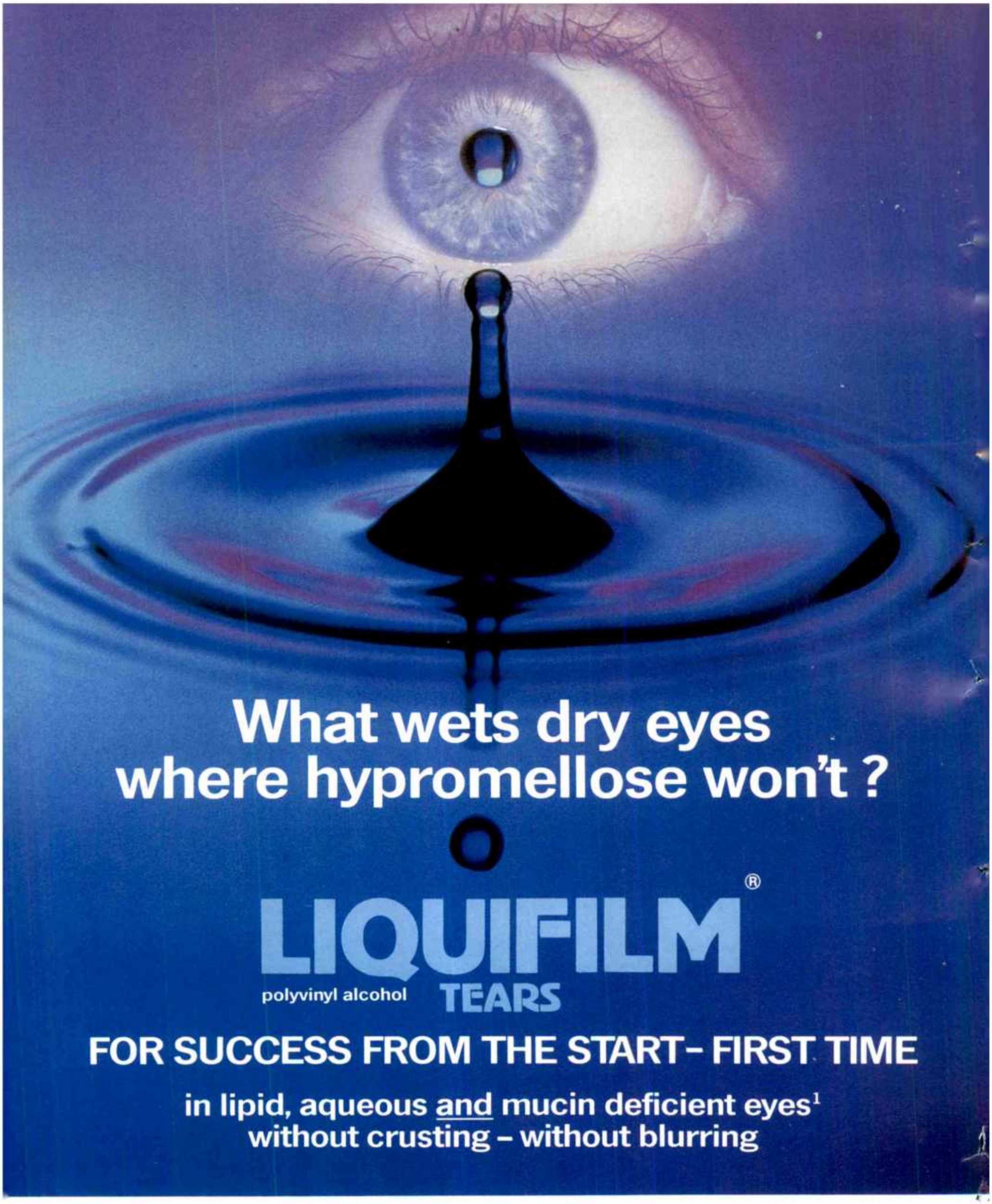
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Incidence of keratoconus in spring catarrh

M DAUD KHAN, NIAMATULLAH KUNDI, NASIR SAEED, ARIFA GULAB, AND ANISA F NAZEER

From the Lady Reading Hospital and Postgraduate Medical Institute, Peshawar, and the Khyber Hospital, Peshawar, Pakistan

SUMMARY Five hundred and thirty cases of spring catarrh were studied at the Department of Ophthalmology, Khyber Hospital Peshawar, Pakistan. Corneal complications occurred in 259 patients, of which 48 cases were of keratoconus, consisting of 41 male and seven female patients. Most of the patients affected (37) were between the ages of 10 and 30 years. Six patients developed acute hydrops, which in one case affected both eyes, though after an interval of a few months. Keratoconus was progressive in many patients, resulting in gross visual loss, often not correctable with glasses or contact lenses and thus requiring keratoplasty. The importance of association of keratoconus with atopic disorders is discussed and its association with spring catarrh is stressed.

Keratoconus is a connective tissue disorder associated with bilateral thinning, scarring, and conical ectasia of axial or periaxial cornea accompanied by painless visual loss.[1] Although it may be associated with a number of local and systemic disorders, its exact pathogenesis is still not clear.[2] The association of keratoconus with atopic conditions has been reported on many occasions.[3-5] Such clinical impressions have been substantiated by immunological disturbances such as significantly raised levels of total or specific IgE in serum.[6] Hayfever, asthma, and eczema are reported to be usual atopic states associated with keratoconus.[2-4] Keratoconus is also known to be associated with spring catarrh,[5 7 8] but such an association has been comparatively less frequently reported.

Material and methods

Five hundred and thirty cases of spring catarrh were studied at the Department of Ophthalmology, Khyber Hospital, Peshawar, from January 1982 to December 1984. Cases included were those that attended the hospital and one of the author's private clinic. The relevant details of history and clinical examination of the patients were recorded on a specially designed proforma. Examination included the usual methods of retinoscopy, ophthalmoscopy, and biomicroscopy. Patients with keratoconus were also examined with keratoscopes. Intraocular pressures were usually checked with Perkins' hand held applanation tonometer. The findings were analysed at the end of the period, and we report here our results on the incidence of keratoconus in the present series of patients with spring catarrh.

Results

Forty eight patients (7% of the total number with spring catarrh) had keratoconus, of which 41 were male and seven female. The maximum number of patients occurred between the ages of 11 and 30 years (Table 1). No patients were below age 5 or over 35. The peak frequency of patients affected was for those who had suffered with symptoms of spring catarrh for six to 10 years (Table 2).

The number of patients in this group who had other associated personal or familial allergies was 17; six had other personal allergies (all hayfever) and 11 had a family history of allergies (Table 3). 92% of patients had mixed lesions, as do most patients with spring catarrh in the region.

Topical steroids were the commonest medication used in this group (92%), but one patient was taking only antihistaminics. The intraocular pressure appeared to be normal in all cases. Eight patients, seven male and one female, developed acute hydrops. One of them developed it in the second eye at an interval of a few months. Almost all settled down with conservative treatment, and many of them regained visual acuity of 6/18–6/24.

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Table 1 *Age distribution of keratoconus among patients of spring catarrh*

Age in years	*No.*	*%*	*Male:female*
0–5	0	0	–:–
6–10	5	10·4	3:2
11–15	11	23·0	11:0
16–20	17	35·5	14:3
21–25	9	18·7	9:0
26–30	4	8·3	4:0
31–35	2	4·1	0:2
Total	48	100·0	41:7

Table 2 *Duration of spring catarrh*

Duration in years	*No. of patients*	*%*
0–5	13	27·1
6–10	19	39·6
11–15	15	31·2
16–20	1	2·1
over 20	—	—
Total	48	100·0

Table 3 *Allergies (familial and personal other than spring catarrh) among patients with keratoconus*

Type of allergy	*No.*	*%*	*Male:female*
Personal	48	100·0	41:7
Spring catarrh	48	100·0	41:7
Hayfever	6	12·5	5:1
Familial	9	18·8	6:3
Spring catarrh	7	14·6	4:3
Asthma and hayfever	1	2·1	1:0
Eczema	1	2·1	1:0

Table 4 *Best correctable visual acuity in eyes with keratoconus*

Visual status	*No. of eyes*	*%*
HM–6/60	39	43·8
6/60–6/24	20	22·5
6/18	10	11·5
6/12	13	14·6
6/9	4	4·5
6/6 (after keratoplasty)	3	3·4
Total	89	100·0

Bilateral keratoconus occurred in the majority (41 cases); seven patients had only one eye involved, the other eye showing no signs of either keratoconus or high astigmatism. Of the 89 eyes affected with keratoconus 38 were legally blind, with a visual acuity of 6/60 or less, while 20 eyes had marked visual handicap with a vision of more than 6/60 but less than 6/24. After keratoplasty three eyes achieved corrected visual acuity of 6/6 with glasses, while one eye achieved 6/18 with glasses (Table 4).

Twenty six eyes showed early signs of keratoconus with corrected visual acuity (with glasses) ranging from 6/9 to 6/18. Owing to its high expense the facility of contact lenses could be extended to only a few individuals. Five patients had undergone keratoplasty, of whom three achieved corrected visual acuity of 6/6, one 6/18, and one had graft rejection twice. The facility of keratoplasty could also be offered to very few patients because of chronic shortage of donor material.

Discussion

Ridley first drew attention to the wide variety of atopic conditions associated with keratoconus.[9] Copeman confirmed these findings.[10] It was also Ridley who first noticed the prevalence of eye rubbing in keratoconus and reported it in 70% of his cases.[11] Karseras and Ruben confirmed this in 1976.[12] Since then an association between atopic states, eye-rubbing and keratoconus has been reported by many workers.[11,13] These clinical findings have also been confirmed by noting biochemical changes in the form of a high incidence of raised total serum IgE and serum specific IgE in patients with keratoconus.[2,6,14]

The usual atopic states reported to be commonly associated with keratoconus are hayfever, asthma, and eczema.[3-8] Its association with spring catarrh has also been noted and reported.[5,7,8] On the other hand not a single case was reported in two large studies on keratoconus.[2,12]

In our study of 530 cases of spring catarrh we found a 7% incidence of keratoconus (41 male and 7 female), of which eight cases developed acute hydrops (seven male and one female). This is almost in agreement with the findings of Gormaz and Eggers,[5] who noted an increased tendency to acute hydrops in their series; they also remarked on a significant male preponderance. We did not find any marked male preponderance, as there was a general male preponderance among patients with spring catarrh in a ratio of 5:1, while the ratio among patients with keratoconus and spring catarrh was 6:1. However, these findings are in disagreement with the marked female preponderance generally reported in patients of keratoconus.[15,16]

All patients of keratoconus in this study were suffering from spring catarrh, but besides this a number of other atopic conditions were found in the patients or their family members (Table 3). All patients had a normal intraocular pressure, and, though all of them received strong steroids at one time or another, none developed a subsequent marked rise of pressure. Raised pressure was, however, noted in patients with keratoconus by von Graefe in 1868, and chronic simple glaucoma was noted by d'Ermo in 1953 and Sbordone and de

Simone in 1957.[17]

Keratoconus has been associated with a familial pattern of inheritance. Both dominant and recessive traits have been reported; consanguinity has also been blamed in some such cases.[16] In our study we found only one case of spring catarrh with keratoconus, a patient who had a brother also suffering from spring catarrh with keratoconus; none of our other patients in this study gave any history of keratoconus among family members. This is a very small number considering that most marriages in our part of the world take place among near relatives, especially first cousins. We also did not note any other congenital anomalies among these patients in this study—for example, Down's syndrome or collagen disorders. This leaves us only with the theory of eye rubbing secondary to the intense irritation caused by the severe mixed type of spring catarrh that we see in the region.

This work was supported by the Pakistan Medical Research Council.

References

1 Bron AJ, Tripathi RC, Harding JJ, Crabbe MJC. Stromal loss in keratoconus. *Trans Ophthalmol Soc UK* 1978; **98**: 393–6.
2 Rahi A, Davies P, Ruben M, Lobascher D, Menon J. Keratoconus and coexisting atopic disease. *Br J Ophthalmol* 1977; **61**: 761–4.
3 Galin MA, Berger R. Atopy and keratoconus. *Am J Ophthalmol* 1958; **45**: 904.
4 Spencer WA, Fisher JJ. The association of keratoconus with atopic dermatitis. *Am J Ophthalmol* 1959; **97**: 332–4.
5 Gormaz A, Eggers C. Vernal keratoconjunctivitis and keratoconus. *Am J Ophthalmol* 1984; **96**: 555–6.
6 Kemp EG, Lewis EJ. Immunoglobulin patterns in keratoconus with particular reference to total and specific IgE levels. *Br J Ophthalmol* 1982; **66**: 717–20.
7 Bietti GB, Ferraboschi C. L'association du catarrhe printanier et du keratocone et son evidence statistique. *Bull Mem Soc Fr Ophtalmol* 1958; **71**: 185–98.
8 Tabbara KP, Butrus SI. Vernal keratoconjunctivitis and keratoconus. *Am J Ophthalmol* 1983; **95**: 704–5.
9 Ridley H. Contact lenses in the treatment of keratoconus. *Br J Ophthalmol* 1956; **40**: 295–304.
10 Copeman PW. Eczema and keratoconus: *Br Med J* 1965; ii: 977–9.
11 Ridley H. In: *Contact lenses symposium*. New York, Basle: Karger, 1966: 163–73.
12 Karseras AG, Ruben M. Aetiology of keratoconus. *Br J Ophthalmol* 1976; **60**: 522–5.
13 Coyle JJ. Keratoconus and eye rubbing. *Am J Ophthalmol* 1984; **97**: 527–8.
14 Easty DL, Entwhistle C, Funk A, Witcher J. Herpes simplex keratitis and keratoconus in atopic patients: a clinical and immunological study. *Trans Ophthalmol Soc UK* 1975; **95**: 267–86.
15 Sorsby A, ed. *Modern ophthalmology*. 2nd ed. London: Butterworth, 1972: **3**: chapter 1: 244.
16 Franschetti A. Keratoconus. In: King JH Jr, Metigne JW, eds. *The cornea: World Congress*. London: Butterworth, 1965: 157.
17 Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1965: **8** (2): chapter 7: 964–76.

Accepted for publication 27 November 1986.

British Journal of Ophthalmology, 1988, 72, 44–49

Contrast sensitivity and acuity relationship in strabismic and anisometropic amblyopia

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SUMMARY The contrast sensitivity function (CSF) and visual acuity were determined in children and adults with unilateral amblyopia due to strabismus or anisometropia with central fixation. The preschool children were examined repeatedly during occlusion treatment. All amblyopes had CSF deficits. The CSF was characterised by its peak value (the maximal sensitivity, S_{max}, and the spatial frequency at which S_{max} occurs, Fr_{max}) calculated by a single peak least-square regression method. The two amblyopic groups showed discrepancies in relationship of both S_{max} and Fr_{max} versus visual acuity both initially and during treatment. The strabismic cases had a more marked visual acuity deficit in relation to the contrast sensitivity losses, whereas these parameters are affected similarly in anisometropic amblyopes. The relationship between recovery of visual acuity and CSF during the initial month of occlusion treatment was of prognostic significance for the outcome of visual acuity improvement.

Amblyopia is defined as an optically uncorrectable loss of vision, usually monocular, without demonstrable pathology in the posterior pole of the eye. This condition develops in early childhood and it affects up to 5% of the population. It is usually connected with strabismus or anisometropia. This visual degradation is treatable during childhood and the common treatment is occlusion therapy. The 'better' eye is occluded for longer or shorter periods.

Amblyopia has been studied by psychophysical tests in humans and in both psychophysical and electrophysiological tests in animals. Although there are great differences in the duration of critical or sensitive periods between animals and humans, animal models can provide a useful conceptual framework to follow. Furthermore, several behavioural aspects of amblyopia in the monkey are similar to human amblyopia in terms of aetiology, severity, and occurrence during a period early in life when the visual system is susceptible to abnormal input.[1-3]

In 1974 Ikeda and Wright suggested that the common aetiological basis for ambylopia caused by anisometropia and strabismus may be 'blur'.[4] In an anisometropic pair of eyes one of the eyes probably receives an input with deprived form and contour. There is no evidence that a strabismic eye receives a blurred image, whereas several studies indicate that abnormal binocular interaction is present in strabismus. The results from psychophysical studies in humans indicate that a common explanation for these two types of amblyopia[5-8] is unlikely.

Studies of the effect of illumination[8] on contrast sensitivity function (CSF) and apparent suprathreshold contrast[9,10] in the two groups have indicated differences in the dysfunction in amblyopia due to strabismus and anisometropia. A threshold contrast comparison between these two groups also indicates differences.[11,12] In general, the CSF from a patient with strabismic amblyopia is affected in the high frequency part, while the anisometropic patients have a CSF depressed over the whole frequency spectrum. These data support a theory whereby strabismic amblyopes have deficits mainly caused by spatial distortion in the central visual field while anisometropic amblyopia is caused by a generally impaired resolution.[13]

In this study we have used a statistical method, U-shaped regression,[14] to determine the maximum contrast sensitivity (S_{max}) and the spatial frequency at which it occurs (Fr_{max}) in order to characterise the CSF. This method has proved to be a useful tool for

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evaluating CSF (Abrahamsson *et al.*, in preparation). The aim of this study was to point out the differences in the threshold contrast sensitivity in relation to visual acuity between strabismic and anisometropic amblyopia before and during treatment by occlusion. We also investigated the possibility of predicting the outcome of amblyopia treatment from the initial (during the first month) changes in CSF and visual acuity.

Material and methods

Patients. Ten patients with strabismic amblyopia and 13 patients with anisometropic amblyopia together with 20 controls were examined. The controls were classified into two groups, 12 children (age 5–8 years) and eight adults (age 15–28 years). Anisometropia was defined as a refractive power difference of 1 D or more in either pair of corresponding principal meridians in the two eyes and absence of any manifest deviation as judged by cover test in the primary position. From all patients or their parents informed consent was obtained.

Amblyopia was defined as a visual acuity quotient (the amblyopic eye acuity divided by the contralateral eye acuity) of 0·8 or less. Five of the strabismic amblyopes were children (age 5–8 years), who were examined before, after, and during treatment. The remaining five cases were adults (age 18–25 years). In the anisometropic amblyopia group were eight children (age 5–7 years) who were treated by occlusion and five adults (age 20–35 years).

The patients initially had a full ophthalmological examination, including cycloplegic refraction. All children with anisometropia and all children with strabismus except for one wore spectacles continuously for a period of at least one month before the initial testing. The children were treated thereafter by full-day occlusion of the dominant eye for up to five or six days a week during the initial period. The visual acuity (VA) and CSF were serially measured during the occlusion period, which continued until the maximum improvement was achieved. After the end of treatment the children were followed up by their ordinary ophthalmologist. The post-treatment visual acuity was tested at least one year after completed therapy. Visual acuity was assessed in the children by linear E optotypes (KIFA: Monoyer-Granström) at 5 m with optimal correction. Ophthalmoscopy demonstrated that all the patients had clear media and no observable abnormalities in the posterior pole of the eye.

In all cases selected, fixation was considered central, though unsteady and slightly drifting in some of them.

Apparatus and procedure. Vertical sinusoidal grating was generated on a television display as previously described by Sjöstrand.[12] The space average luminance of the grating was 135 cd/m^2. The television was masked to subtend 1·7×1·7 degrees of visual angle, when viewed at a distance of 4 m. Spatial frequency was varied between 1 and 32 cycles per degree. Pattern contrast was varied in 2 dB steps in the range 0·7 to 0·0007. The contrast sensitivity (reciprocal to contrast) function was determined monocularly by the increasing contrast method.

Each test session started with a visual acuity testing. Then the child had a break as he walked to an other examining room for the CSF test. The CSF was tested by a game where the child chose among glass balls and wooden dolls of different sizes to match the spatial frequency of the grating when it just becomes detectable. Breaks were allowed whenever the child lost interest in the test. All tests were performed by the authors. The children were tested before and repeatedly after the start of the patching.

Statistics. The co-ordinates of the peak of the CSF (maximum sensitivity, S_{max}, and the frequency at which it occurs, Fr_{max}) were calculated by a single peak least square fit estimation.[14] The statistical calculation was based on the assumption that the CSF monotonously rises to a maximum and then monotonously (without local maxima or minima) declines. The CSF cut-off frequency was calculated by extrapolating a linear regression of the high-frequency limb of the CSF to contrast sensitivity level 1·0.

Diagnostic indices. In this explorative study several simple, potentially valuable indices can be calculated (Table 1). To compare these indices with respect to their discriminating ability two limits were determined so that 10% (two out of 20) of the observed normal eyes would exceed these limits. Thus the specificity (the proportion of correctly classified normals) will be approximately 90%. The sensitivity (the proportion of correctly classified patients) in this sample is determined to be the proportion of the observed cases exceeding the limits. The sensitivity values for different indices are reported in Table 1. As could be expected, VA separates amblyopes from controls very well, since acuity is used as the definition of amblyopia.

Other types of diagnostic indices are those where the discrimination is between the different groups of patients. To see how well some diagnostic indices could separate the two amblyopic groups from each other a limit is set for each index so that patients on one side of the limit are classified as strabismic and on the other as anisometropic. The limit for each index is determined in such a way that the percentage of correctly classified strabismic patients equals the percentage correctly classified anisometropic patients, and this common percentage is reported in

Table 2. Tables 1 and 2 together demonstrate two different aspects of a diagnostic index that are equally important.

Results

The distribution of the sensitivity maximum versus acuity of the amblyopic eyes of 23 patients together with 20 normal persons is presented in Fig. 1. The data from the initial test session were used. The data points representing the amblyopic eyes were gathered into two partly separated clusters. The strabismic amblyopes show an S_{max} value rather independent of visual acuity, while in the anisometropic amblyopia there is a clear relationship between visual acuity and S_{max}. In general the S_{max} value for the strabismic group is higher than for the anisometropic amblyopia group.

Since the anisometropic group initially had lower visual acuity levels than the strabismic group, we compared S_{max} for the two groups at three selected visual acuity levels (0·2, 0·3, and 0·5). Seven strabismic patients and 10 anisometropic patients had a visual acuity at at least one of the selected acuity levels at the initial session or at some occasion during treatment. In Fig. 2A the results are presented and the data from each patient are used only once. In comparison the anisometropic group had lower values of S_{max} than the strabismic patients. The distribution of the Fr_{max} (Fig. 2B) at the same acuity levels showed a tendency for a more pronounced shift of the peak towards lower frequencies in the anisometropic group compared with the strabismic group.

The S_{max} calculated from the CSFs obtained during treatment of the children are presented in Fig. 3A.

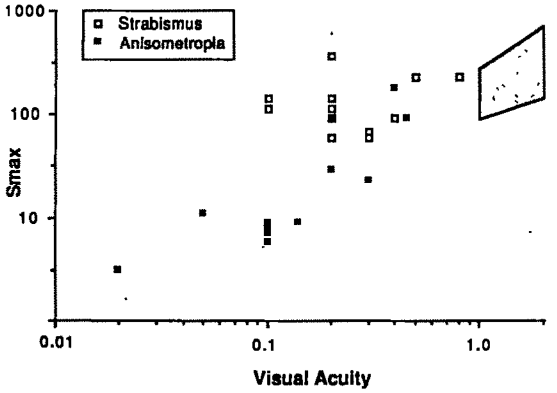

Fig. 1 *The relationship between visual acuity and S_{max} in strabismic and anisometropic amblyopia. The two amblyopic groups are indicated by filled (anisometropia) and open squares (strabismus). The dotted area represents the normal range.*

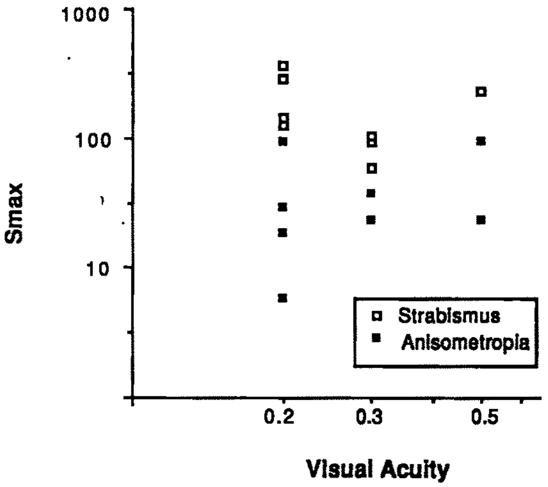

Fig. 2A

The similarity to the data in Figs. 1 and 2 is notable. The anisometropic patients have an increase in both acuity and S_{max}, while the strabismic patients show only an increasing visual acuity. In strabismic cases the S_{max} are at a near normal level independent of the acuity. The Fr_{max} from the same sessions are presented in Fig. 3B. The strabismic group shows less variability in the Fr_{max} during treatment than the anisometropic group. Grating acuity (cut-off frequency in this case) is usually compared with visual

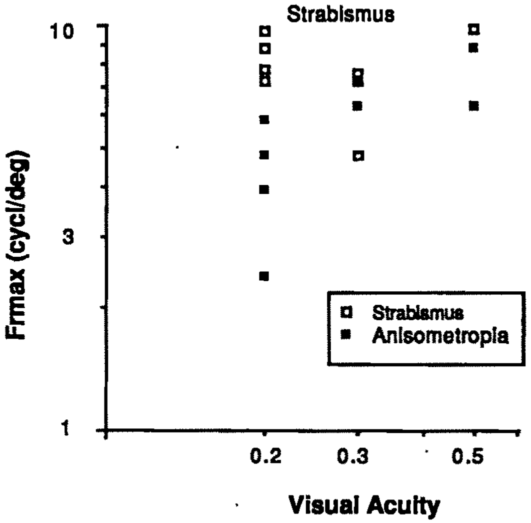

Fig. 2B

Fig. 2 A: *The S_{max} of the two amblyopic groups at three selected visual acuity levels is presented* B: *The Fr_{max} at the same three visual acuity levels are presented. The same symbols as in Fig. 1 are used.*

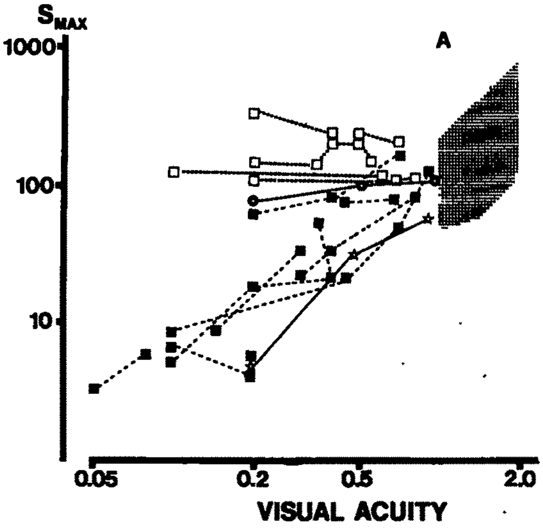

Fig. 3A

acuity by the equation VA=(GA)/30. The results in our study show that cut-off frequencies in general are higher than the visual acuity would predict (results not shown).

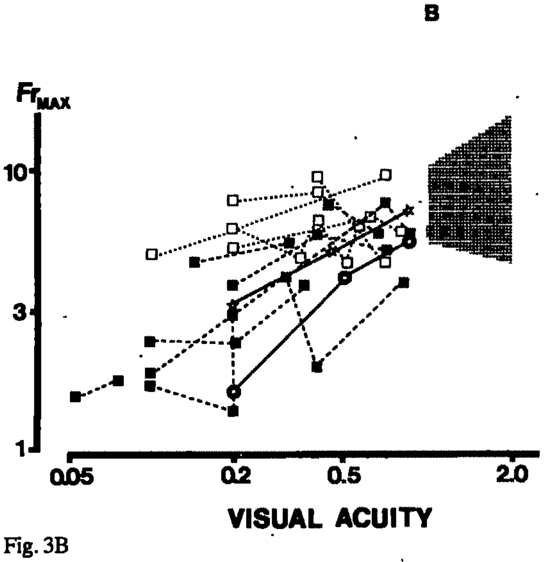

Fig. 3B

Fig. 3 A: *S_{max} versus visual acuity during amblyopia treatment. The data from each patient are connected by a dotted (strabismus) or dashed (anisometropia) line. In all cases the initial value is the one closest to the lower left corner. For the amblyopes the same symbols as in Fig. 1 are used. Stars in circles connected by a solid line indicate a typical retinal detachment patient during recovery, and stars connected by a solid line indicates data from a typical case of optic neuropathy during recovery. The normal range is indicated by the dotted area* B: *The same symbols are used where the FR_{max} versus visual acuity is presented.*

Table 1 *The ability of dignostic indices to separate amblyopic patients from normals measured as a percentage of correctly classified amblyopes and normals*

Visual acuity	100
S_{max}	56
$S_{max}/\sqrt{VA}$	84
Cut-off frequency	72
Cur-off frequency/$\sqrt{VA}$	96

Table 2 *The ability of diagnostic indices correctly to classify strabismic and anisometropic amblyopia: the percentage correctly classified amblyopes*

Visual acuity	62
S_{max}	62
$S_{max}/\sqrt{VA}$	76
Cut-off frequency	58
Cut-off frequency/$\sqrt{VA}$	58

Visual acuity, S_{max}, and cut-off frequency were used to calculate diagnostic indices. In Table 1 the ability of different diagnostic indices to separate normals from amblyopes is presented. Since visual acuity loss is used in the definition of amblyopia and a VA of 1·0 or better is a part of the definition of normals we found, as can be expected, that VAs classify all amblyopes and normals (100%) correctly. The two CSF parameters (S_{max}, cut-off frequency) had lower diagnostic ability to differentiate amblyopes from controls. Table 2 indicates the ability of diagnostic indices to separate the two groups of amblyopes from each other. We found that $S_{max}/\sqrt{VA}$ was the index that best separated the two groups of amblyopes from each other (76% of the amblyopes were correctly classified as strabismic or anisometropic amblyopia). The same index has been used to separate patients with retinal detachment from those with optic neuropathy (Abrahamsson *et al.*, in preparation).

The changes in visual acuity and CSF (represented by S_{max} and cut-off frequency) in the initial phase (first month) of the occlusion therapy have been studied. A high end-of-treatment visual acuity was the criterion we used to define a successful treatment. In four cases there was an acuity loss between end of treatment and the time at which the posttreatment acuity was obtained.

In Fig. 4 we have expressed the initial acuity changes as the percentage of increase of letter and grating acuity between the pretreatment values and the acuities obtained after one month of treatment. With this construction the number 0 indicates that the value obtained after one month is equal to the initial value and 100 means a doubling of the initial value. The data indicate that prognosis for a successful occlusion therapy improves as the VA percentage

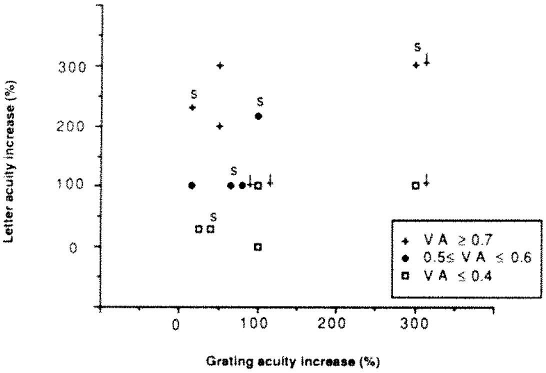

Fig. 4 *The changes in VA and GA during the first month of occlusion therapy. The increase in letter and grating acuity during the first month is calculated as a percentage where 100 indicates that the value measured after one month of treatment is twice the initial value. The data are classified into three groups according to the visual acuity at the end of treatment. The four patients with a post-treatment letter acuity lower than the end of treatment acuity are marked with an arrow, and the strabismic cases are marked with an* S.

becomes comparably larger than the GA percentage, since all patients with a visual acuity ≥0·5 at the end of treatment fulfilled the criteria VA versus GA increasing ratio ≥1·0.

In all four cases with an acuity loss during the period following the end of treatment and the final evaluation of post-treatment letter acuity the letter versus grating acuity increasing ratio was ≤1·1.

Owing to the small sample size and the differences in mean pretreatment visual acuity between the groups it was not possible in our small sample to find any relationship between the letter and grating acuity increase and age or type of amblyopia.

Discussion

Several studies have shown that there are discrepancies in CSF obtained in strabismic or anisometropic[5 11 12] amblyopes. Strabismic amblyopia is generally characterised by a high-frequency decrease in the CSF, while the CSFs of anisometropic patients are affected at all spatial frequencies. A difference in the apparent suprathreshold contrast between the two groups has also been reported.[9 10] In this study we have pointed out specific CSF discrepancies between the two groups. In strabismic patients the maximum point of the CSF is relatively uncorrelated with the visual acuity level. Even when the visual acuity is markedly reduced, the CSF curve is essentially normal from low frequencies to the maximum point, while the steepness of the high-frequency limb varies. The anisometropic amblyope generally has a CSF that is subnormal at all spatial frequencies. The maximum point is markedly shifted towards lower frequencies, and as acuity decreases the sensitivity declines simultaneously. There is no obvious relationship between S_{max} from the initial testing versus visual acuity from the same session in strabismic amblyopes whereas a clear relation is demonstrable in the anisometropic amblyopes (Fig. 1). When we study individual cases during treatment, this phenomenon, discrepancy in the $S_{max}/\sqrt{VA}$ relation, is clearly shown (Fig. 3).

The use of the data from the initial test session can introduce a systematic error, since the untreated anisometropic amblyopes in general had a lower visual acuity than the untreated strabismic amblyopes. In order to get a fair estimation of the differences in the VA versus S_{max} relation between the two groups we selected three visual acuity levels (Fig. 2). This analysis showed no significant differences between the results in Figs. 1 and 2 and confirmed the discrepancy between the two groups of amblyopes. The S_{max} of the anisometropic patients at a given acuity level is thus generally lower than that of the strabismic patients. There is a preferential loss of VA in strabismic amblyopia that resembles the vernier discrimination data presented by several authors.[6 13 15 16] These reports suggested that spatial distortion is the primary cause of the loss of visual acuity in strabismic amblyopia. In anisometropic amblyopia spatial distortion can be demonstrated, but impaired resolution seems to be the major factor.

In a study (in preparation) we found that some of the parameters of central vision used in this study (S_{max}, Fr_{max}, and VA) are useful in separating two groups of patients with retinal detachment and optic neuropathy respectively. Similarly, these parameters can be used as diagnostic indices for differentiating between two subgroups of amblyopia in the present study (Tables 1, 2). The relationship between S_{max} and VA in the strabismic patients data are similar to those of the retinal detachment patients, and the data of the anisometropic patients correspond to those of the patients with optic neuropathy. These findings concur with those of other studies[5-8] showing that there are differencies in the neural basis of the two forms of amblyopia. Our present results, however, do not contradict the theory proposed by Flom and Bedell[17] and supported by Hess and Pointer[18] that the strabismic patients have abnormalities mainly in the central visual field, and the anisometropic amblyopia affects the whole visual field.

The relationship between the changes in VA and cut-off frequency during the first month of treatment and final visual acuity obtained at the end of the occlusion therapy have been used to study the possibility of establishing criteria for prognosis in relation to treatment. We found that a high VA at the end of treatment was correlated with a rapid and marked increase of the letter acuity during the first month of treatment. The data presented in Fig. 4 for the first month of treatment also indicate that a relative VA increase greater than the relative GA increase is correlated with a favourable prognosis. In all amblyopic patients with a post-treatment (obtained at least one year after end of treatment) VA of 0·5 or better the relative VA increase is greater than the relative GA increase. All patients with post-treatment VA<0·5 and all patients with acuity loss after treatment ended were in the group with a relative VA increase less or approximately equal to the relative GA increase.

Our data indicate that the CSF versus acuity relationship gives some prediction of the outcome of occlusion therapy in individual amblyopic patients. One of the important factors seems to be the acuity change during the first month of treatment. The relation cut-off frequency change versus VA change ought to be evaluated only in those cases where there is no or a limited increase in VA during the first month. A small GA relative to the visual acuity increase during the first month seems to correlate with better end-of-treatment VA than does a large GA increase in combination with the same acuity increase. The same conclusion has been presented by Dale,[19] who studied the relationship between acuity obtained by single letters and linear acuity.

In summary, there are differences in the CSF and even more pronounced differences in the relation VA versus CSF between anisometropic and strabismic amblyopia. These differencies can also be demonstrated in individual cases during treatment The findings support the theories which claim that there are differences in the neural basis of functional impairment in these two conditions. We have also found that the changes of CSF and acuity during the first month of treatment are predictive of the outcome of the occlusion therapy.

This study was supported by the Swedish Medical Research Council (grant 02226), Handlanden H Svensson Foundation, and the Carmen and Bertil Régner Research Foundation. We will also thank Marianne Frisén for statistical assistance and Dr K Norrsell for valuable advice and constructive criticism.

References

1 Blakemore C, Vital-Durand F. Development of the neural basis of visual acuity in monkeys. Speculation on the origin of deprivation amblyopia. *Trans Ophthalmol Soc UK* 1979; **99:** 363–8.

2 von Noorden GK, Dowling JE. Experimental amblyopia in monkeys II. Behavioral studies in strabismic amblyopia. *Arch Ophthalmol* 1970; **84:** 215–20.

3 Smith III EL, Harwerth RS, Crawford MLJ. Spatial contrast sensitivity deficits in monkeys produced by optically induced anisometropia. *Invest Ophthalmol Vis Sci* 1985; **26:** 330–42.

4 Ikeda H, Wright MJ. Is amblyopia due to inappropriate stimulation of the sustained pathway during development. *Brit J Ophthalmol* 1974; **58:** 165–75.

5 Hess RF, Howell ER. The threshold contrast sensitivity function in strabismic amblyopia: Evidence for a two type classification. *Vision Res* 1977; **17:** 1049–55.

6 Levi DM, Klein S. Differences in vernier discrimination for gratings between strabismic and anisometropic amblyopes. *Invest Ophthalmol Vis Sci* 1982; **23:** 398–407.

7 Hess RF, Bradley A, Piotrowski L. Contrast-coding in amblyopia I. Differences in neural basis of human amblyopia. *Proc R Soc Lond (Biol)* 1983; **217:** 309–30.

8 Hess RF, Campbell FW, Zimmern R. Differences in the neural basis of human amblyopias: The effect of mean luminance. *Vision Res* 1980; **20:** 295–305.

9 Hess RF, Bradley A. Contrast perception above threshold is only minimally impaired in human amblyopia. *Nature* 1980; **287:** 463–4.

10 Levi DM, Harwerth RS, Manny RE. Suprathreshold spatial frequency detection and binocular interaction in strabismic and anisometropic amblyopia. *Invest Ophthalmol Vis Sci* 1979; **18:** 714–25.

11 Campos EC, Prampolini ML, Gulli R. Contrast sensitivity differences between strabismic and anisometropic amblyopia: objective correlate by means of visual evoked responses. *Doc Ophthalmol* 1984; **58:** 45–50.

12 Sjöstrand J. Contrast sensitivity in children with strabismic and anisometropic amblyopia. A study of effect of treatment. *Acta Ophthalmol (Kbh)* 1981; **59:** 25–34.

13 Bedell HE, Flom MC. Monocular spatial disorder in strabismic amblyopia. *Invest Ophthalmol Vis Sci* 1981; **20:** 263–8.

14 Frisén M. U-shaped regression. *COMPSTAT Proc comput statistics* 1980; **4:** 304–7.

15 Bedell HE, Flom MC, Barbeito R. Spatial aberration and acuity in strabismus and amblyopia. *Invest Ophthalmol Vis Sci* 1985; **26:** 909–16.

16 Stuart JA, Burian HM. A study of separation difficulty. *Am J Ophthalmol* 1962; **53:** 471–7.

17 Flom MC, Bedell HE. Identifying amblyopia using associated conditions: acuity and nonacuity features. *Am J Opt Physiol Opt* 1985; **62:** 153–60.

18 Hess RF, Pointer JS. Differences in the neural basis of human amblyopia. The distribution of the anomaly across the visual field. *Vision Res* 1985; **25:** 1577–94.

19 Dale RT. *Fundamentals of ocular mobility and strabismus*. New York: Grune and Stratton, 1982: 132–60.

Accepted for publication 27th November 1986.

British Journal of Ophthalmology, 1988, 72, 50–54

Grating and recognition acuities of young amblyopes

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SUMMARY The visual acuities of 36 young amblyopes were determined by (*a*) conventional recognition tests (near and distance) and (*b*) an adapted grating acuity card procedure. Considerable agreement between the estimates of acuity obtained with each method was demonstrated, which was generally less than, or equal to, the mean difference between adjacent Snellen lines (4·5 c deg^{-1}). Estimates of grating acuity obtained with vertical gratings did not differ significantly from those obtained with horizontal gratings. There was no difference between the subjects' ability to detect the grating (acuity) and accurately to discriminate target orientation (horizontal or vertical). The results of the experiment are discussed in relation to previous findings of a discrepancy between grating and recognition acuities in amblyopia, and the clinical use of the acuity card procedure.

The observation that infants will preferentially fixate a patterned rather than a 'blank' or homogeneous surface[1] has spawned a variety of behavioural tests of infant visual acuity. Procedures such as forced-choice preferential looking (FPL) and operant preferential looking (OPL) have been used to study normal visual development[2-7] and abnormalities of vision in infants and young children.[8-11] The assessment of visual acuity by preferential looking procedures typically involves the simultaneous presentation of a grating pattern and a homogeneous field of equal space-average luminance. An observer, who is unaware of the position of the stimulus, judges from the infant's looking behaviour whether the grating has been detected. The observer's responses are used to generate a psychometric function from which an estimate of the infant's visual acuity can be obtained. With identical grating targets these procedures can be adapted for use with older children, target detection being signalled by pointing or verbal identification.

Vision tests based on preferential looking have until recently been restricted to laboratory use and have not been employed for routine clinical assessment. The often sophisticated nature of the apparatus required to present the grating stimuli and the need to present a large number of trials to obtain a reliable measure of acuity have limited their clinical application. Recently, however, a new 'acuity card procedure'[12] has been developed which may be particularly suitable for routine orthoptic or ophthalmological use. Acuity cards are photographically reproduced square-wave gratings mounted in cardboard frames. The experimenter determines the visual acuity by observing the highest spatial frequency target to which a behavioural response (for example, pointing, eye, and head movements) is elicited. Lengthy psychophysical procedures are not involved. Despite its apparent lack of sophistication the acuity card procedure yields acuity age norms equivalent to those obtained with other more complex forced choice methods and has small inter-observer test-retest differences[13] (Dobson V, Schwartz TL, personal communication).

The assessment of vision with grating targets may be a particularly suitable means of monitoring visual function in young amblyopes undergoing therapy. The use of standard recognition tasks is often inappropriate with an uncooperative, shy, or poorly motivated child or for one who is unable to respond to conventional optotypes. However, there is some evidence to suggest that grating acuities may considerably overestimate recognition acuities in amblyopia; that is, normal grating acuities (6/6 Snellen equivalents) can be recorded in subjects whose recognition acuities are markedly impaired.[14] One explanation for this finding is the spatial distortion of vision reported in amblyopia[15] that would be expected to differentially impair recognition acuity. If the disparity between recognition and grating acuities is consistently large, it may be inappropriate to assess amblyopic vision with grating targets.

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Previous use of the acuity card procedure has been restricted to neonates and infants (typically less than 3 years old). In this study we evaluate the use of an adapted acuity card procedure in an older group of amblyopic children and compare their grating acuities with those obtained by conventional recognition tests.

Materials and method

Thirty-six children ranging in age from 4·4 to 9·3 years (mean 6·3 years) were recruited for the experiment and were all attending the Orthoptic Department at the Leicester Royal Infirmary. The diagnostic categories of amblyopia in which they were placed were strabismic (17), anisometropic (6), and anisometropic and strabismic (13). The experiment was performed after a review of their orthoptic treatment. Near and distance recognition acuities were measured before and after the determination of grating acuity by a method appropriate to their age and developmental status (Table 1). Grating acuities were measured by an adapted acuity card procedure in which grating targets paired with a 'blank' field of equal space-average luminance were presented within a rectangular aperture in a cardboard surround (Fig. 1). Trials were administered according to a descending method of limits which involved the repetition of each grating three times with position (left, right) randomised. Ten spatial frequencies were tested ranging from 3 c deg^{-1} (6/60) to 30 c deg^{-1} (6/6). Full details of the grating targets are given in Table 1. Testing was terminated at the highest spatial frequency at which three 'don't know' responses were elicited. Subjects were encouraged not to guess.

A total of three grating conditions were presented in a balanced and randomised experimental design. The first two conditions consisted of a simple detection task of gratings which were either vertically (condition 1) or horizontally (condition 2) orientated. In the third condition both horizontal and vertical gratings were presented, and in addition to detecting the presence of the grating subjects were required to indicate its orientation. A variety of behavioural responses were elicited which most commonly included pointing combined with a verbal response. The orientation discrimination task (condition 3) was included because, during clinical use of the acuity card procedure by one of us (ARF), it had been observed that in some cases a considerable disparity existed between a detection threshold (acuity) and the ability to distinguish accurately the orientation of the grating. All acuity measurements were obtained in the amblyopic eye only, with spectacle correction (if prescribed) worn.

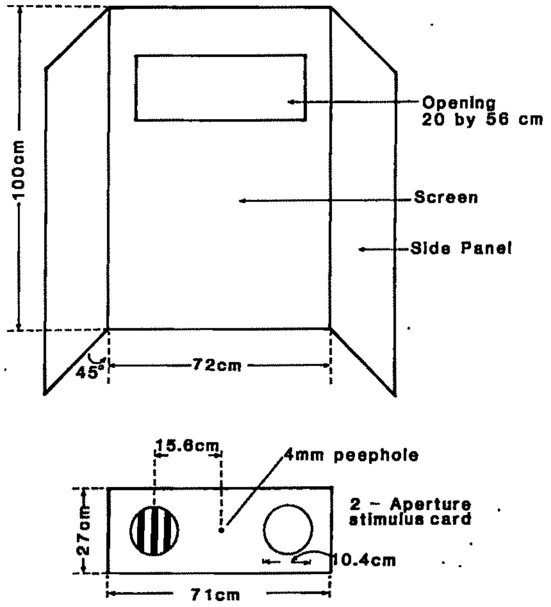

Fig. 1 *The acuity card apparatus: surround and stimulus cards. (After McDonald et al.*[12]*)*

Results

Grating acuities (pooled across horizontal and vertical orientation) were estimated by a logistic

Table 1 *Details of grating and recognition acuity tasks*

Recognition acuity		*Grating acuity*
Near: (0·33 m)	*Distance (6 m)*	
RAF rule (24)	Snellen: linear optotype (25)	Grating targets subtended, 3·0, 4·0, 6·0, 7·5, 10·0, 12·0, 15·0, 20·0, 24·0, and 30 c deg^{-1} at 0·36 m
'Matching' RAF rule (8)	'Matching' Snellen: linear optotype (18)	
Reduced linear Snellen (4)	Sheridan Gardiner: single optotype (3)	Acuity cards were back-illuminated with a single tungsten filament light source. Space-average luminance of targets and 'blank' field was approximately 1·3 log cd m^{-2}

Number of children tested shown in parentheses

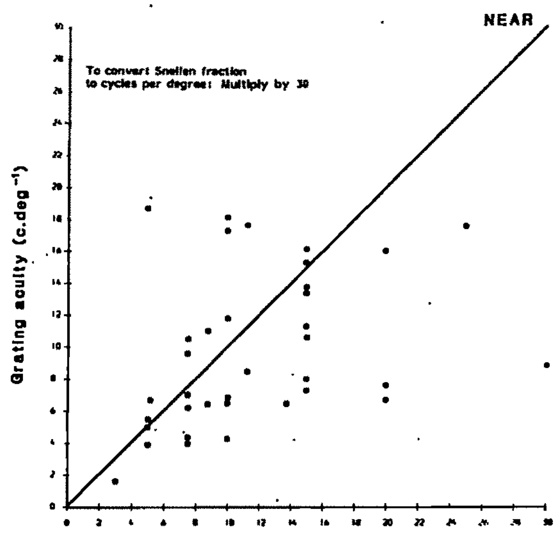

Fig. 2 *Relationship between near recognition acuity and grating acuity.*

model as described in the Appendix. Near and distance recognition acuity were defined as the arithmetic mean of the scores obtained before and after the determination of grating acuity.

The relationship between grating and recognition acuities (near and distance) are shown in Figs. 2 and 3. The 'line of equality' corresponds to the points at which grating and recognition acuities are in perfect agreement. Grating acuity was shown to be significantly correlated with recognition acuity (near: $r=0{\cdot}33$, $p<0{\cdot}05$; distance: $r=0{\cdot}55$, $p<0{\cdot}001$).

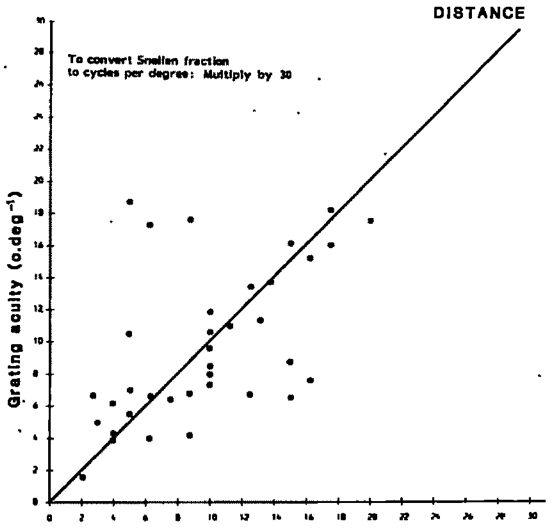

Fig. 3 *Relationship between distance recognition acuity and grating acuity.*

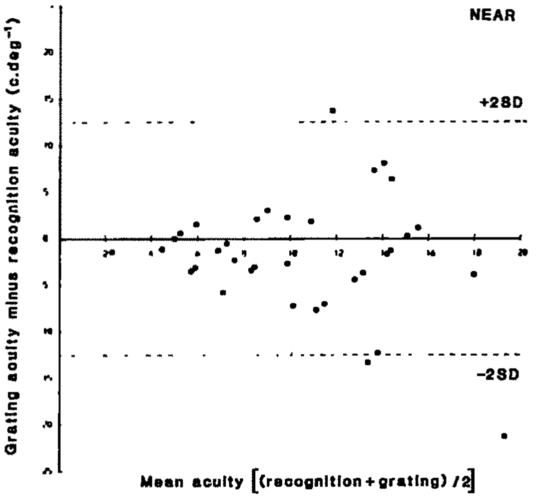

Fig. 4 *Difference between grating acuity and near recognition acuity against mean acuity.*

Although both near and distance recognition acuities are significantly correlated with grating acuity, this finding does not indicate the extent of the *agreement* between the two measures. The difference between agreement and correlation can be appreciated by inspection of the scattergrams shown in Figs. 2 and 3. Measures of recognition and grating acuity scores are in exact agreement only when they lie on the 'line of equality'. However, a high positive correlation would be obtained if the data points formed any straight line with a positive slope. For a further discussion on the inappropriate use of the correlation coefficient when estimating the agreement between two alternative measures the reader is referred to the recent paper by Bland and Altman.[16] The extent of the agreement between grating and recognition acuities is shown in Figs. 4 and 5. The data points show for each child the difference between the grating and recognition acuities plotted against the mean acuity (grating+recognition/2). Perfect agreement is indicated by points falling on the 'zero difference line'—agreement decreasing as a function of the distance between this line and each data point.

The final analysis compared the grating detection thresholds (acuity) with the thresholds obtained for correctly discriminating the orientation of the grating targets (see 'Materials and methods'). A χ^2 test of the change in the log likelihood (see Appendix) failed to reveal any difference between the subjects' ability to detect or discriminate the orientation of the gratings.

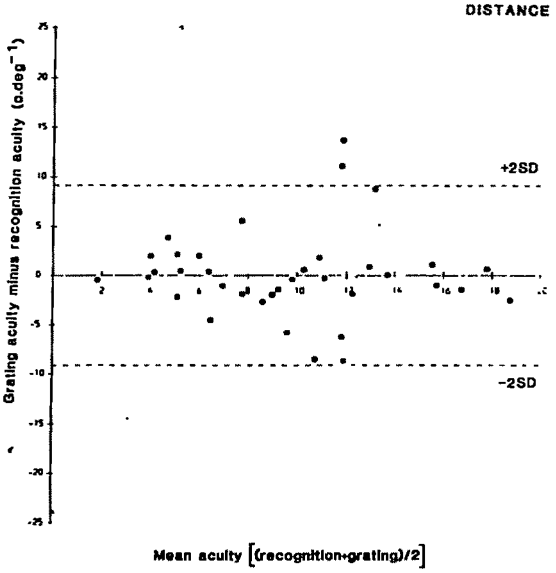

Fig. 5 *Difference between grating acuity and distance recognition acuity against mean acuity.*

Similarly, there were no differences in the grating acuities obtained with horizontal or vertical gratings.

Discussion

If the acuity card procedure is to prove a viable method of routinely assessing visual acuity in amblyopes it must fulfil two criteria. Firstly, grating acuities must relate in some predictable manner to those obtained with conventional methods. Secondly, the ease and length of time taken to administer the test must be in accord with the constraints imposed by clinical use.

The extent of the agreement between grating and recognition acuities is shown in Figs. 4 and 5. Adopting a bandwidth of 4·5 c deg^{-1} (this corresponds to the mean difference between adjacent lines on a standard Snellen chart in the range 6/6 to 6/60) we can see that 24(67%) of the differences between the grating and recognition acuities against the mean acuities fall on or within this bandwidth for near recognition and 28(78%) for distance recognition. Apart from cases in which distance acuity was determined from single optotype characters, the proportion of scores that fall within the 4·5 c deg^{-1} bandwidth rises to 82%—that is, the grating and recognition acuities of 27 out of 33 subjects agreed within one mean Snellen line (single optotypes will frequently overestimate recognition acuity owing to the 'crowding effect' or contour interaction that occurs with line optotypes).[17,18] Doubling this bandwidth to 9 c deg^{-1} that is, twice the mean difference between adjacent Snellen lines, leaves 32(89%) of near recognition acuities and 34(94%) of distance recognition acuities within this bandwidth. These findings show that grating acuities can provide clinically useful estimates of visual acuity which are, in most cases, in good agreement with those obtained by conventional methods.

The results failed to reveal any differences between grating detection thresholds (acuity) and the threshold for correctly discriminating grating orientation. It had been supposed from our previous clinical experience that the orientation discrimination task would prove more difficult. Careful attention was paid to matching the luminance of each grating target with that of the corresponding 'blank' by back-illuminating the acuity cards. Failure to do this could have resulted in the child responding to the brightest aperture in the test card, thus producing a spurious estimate of acuity. Our experience suggests that equating the luminance of the grating targets with the 'blank' field is an important prerequisite for the efficient administration of the acuity card procedure. Incorporating an orientation discrimination task into the acuity card procedure may be one safeguard to prevent subjects from responding to differences in luminance when presented with a subthreshold grating target.

Our results do not confirm previous findings[10,14] that grating acuities will significantly overestimate recognition acuity—none of our sample of amblyopic children was found to possess a normal grating acuity i.e 30 c.deg^{-1}. However, the threshold criterion for grating acuity (probability of correct detection =95%, see Appendix) was deliberately set to a high level. This ensured that grating acuity was appropriately equated with the high level of certainty with which the recognition acuities were obtained in this study and indeed in standard clinical practice. Using a slightly less rigorous (80%) criterion, Jenkins and co-workers[19] have also demonstrated the predictive value of grating acuity in the assessment of amblyopic vision. In clinical practice however, the subjective method of analysis of the acuity card procedure may increase the likelihood of grating acuities exceeding those obtained with a recognition task.

In this study grating acuities were determined by two orthoptists with considerable experience in measuring visual acuity in young children. In their opinion the adapted acuity card procedure was easy to administer, and frequently a more rapid response was elicited from the child presented with the acuity cards than when presented with a recognition target. The test procedure for determining grating acuities in the present experiment differed from that originally described. Here, acuities were obtained with a descending method of limits in order that the possible differences in thresholds for gratings of different orientations could be accurately determined. (In the original version of the test the examiner is free to choose which gratings to present and the estimate of acuity is based on their subjective opinion of the infant's behaviour.) This adaptation inevitably increased the time taken to administer the test, though it was apparent that, had the original acuity card procedure been adhered to, an estimate of acuity could have been obtained in 2 to 3 minutes.

APPENDIX

The modified logistic model

The usual logistic model for analysing binary data assumes that there exists a threshold above which the subject's response is correct and below which it is incorrect. When performing the experiment the examiners noticed that despite counter instruction many of the children appeared to guess the position of the grating, an observation supported by the number of incorrect replies given. To allow for this in the analysis the logistic model was modified to allow for three responses, namely 'correct', 'incorrect', and 'don't know'.

The modified logistic model assumes that there exist thresholds q_0 and q_1. Below q_0 the response is 'correct', between the two the subject guesses and thus has an equal chance of being 'correct' or 'incorrect', and above q_1 the response is 'don't know'.

If F represents the distribution function of the logistic distribution the probabilities of the three possible responses may be expressed as,

$$\text{Prob. (correct)}=1/2\,[F(q_1-by)+F(q_0-by)],$$
$$\text{Prob. (incorrect)}=1/2\,[F(q_1-by)-F(q_0-by)],$$
$$\text{Prob. (don't know)}=1-F(q_1-by),$$

where y is the size of the grating under test and b is a scale parameter.

The parameters q_0, q_1, and b were estimated by the method of maximum likelihood, and the grating acuity y_0 of the subject was defined as that grating that they would have correctly located on 95% of tests. That is to say,

$$1/2\,[F(q_1-by_0)+F(q_0-by_0]=0{\cdot}95.$$

The authors acknowledge the co-operation of Ms Elizabeth Bacon in providing the facilities in the Orthoptic Department at the Leicester Royal Infirmary, and the helpful comments provided by Dr Luisa Mayer on a previous draft of this paper.

References

1 Fantz RL. Pattern vision in young infants. *Psychological Record* 1958; **8:** 43–7.

2 Teller DY, Morse R, Borton R, Regal D. Visual acuity for vertical and diagonal gratings in human infants. *Vision Res* 1974; **14:** 1433–9.

3 Dobson V, Teller DY, Belgum J. Visual acuity in human infants assessed with stationary stripes and phase-alternated checkerboards. *Vision Res* 1978; **18:** 1233–8.

4 Atkinson J, Braddick O, Pimm-Smith E. 'Preferential looking' for monocular and binocular acuity testing of infants. *Br J Ophthalmol* 1982; **66:** 264–8.

5 Mayer DL, Dobson V. Assessment of vision in young children: a new operant approach yields estimates of acuity. *Invest Ophthalmol Vis Sci* 1980; **19:** 566–70.

6 Mayer DL, Dobson V. Visual development in infants and young children as assessed by operant preferential looking. *Vision Res* 1982; **22:** 1141–51.

7 Sokol S, Moskowitz A. Comparison of pattern VEPs and preferential-looking behaviour in 3-month-old infants. *Invest Ophthalmol Vis Sci* 1985; **26:** 359–65.

8 Jacobson SG, Mohindra I, Held R. Visual acuity of infants with ocular diseases. *Am J Ophthalmol* 1982; **93:** 198–209.

9 Mayer DL, Fulton AB, Hansen RM. Preferential looking acuity obtained with a staircase procedure in pediatric patients. *Invest Ophthalmol Vis Sci* 1982; **23:** 538–43.

10 Mayer DL, Fulton AB, Rodier D. Grating and recognition acuities of pediatric patients. *Ophthalmology* 1984; **91:** 947–53.

11 Mayer DL, Fulton AB. Preferential looking grating acuities of infants at risk of amblyopia. *Trans Ophthalmol Soc UK* 1985; **104:** 903–11.

12 McDonald M, Dobson V, Sebris SL, Baitch L, Varner D, Teller DY. The acuity card procedure: a rapid test of infant visual acuity. *Invest Ophthalmol Vis Sci* 1985; **26:** 1158–62.

13 Teller DY, McDonald M, Preston K, Sebris SL, Dobson V. Visual acuity in infants and children: the acuity card procedure. *Dev Med Child Neurol* 1986; **28:** 779–89.

14 Howell ER, Mitchell DE, Keith CG. Contrast thresholds for sine gratings of children with amblyopia. *Invest Ophthalmol Vis Sci* 1983; **24:** 782–7.

15 Hess RF, Campbell FW, Greenhalgh T. On the nature of the abnormality in human amblyopia; neural aberrations and neural sensitivity loss. *Pflügers Arch* 1978; **377:** 201–7.

16 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i:** 307–10.

17 Stuart JA, Burian HM. A study of separation difficulty; its relationship to visual acuity in normal and amblyopic eyes. *Am J Ophthalmol* 1962; **53:** 471–7.

18 Keith CG, Howell ER, Mitchell DE, Smith S. Clinical trial of the use of rotating grating patterns in the treatment of amblyopia. *Br J Ophthalmol* 1980; **64:** 597–606.

19 Jenkins PL, Simon JW, Kandel GL, Forster T. A simple grating acuity test for impaired children. *Am J Ophthalmol* 1985; **99:** 652–8.

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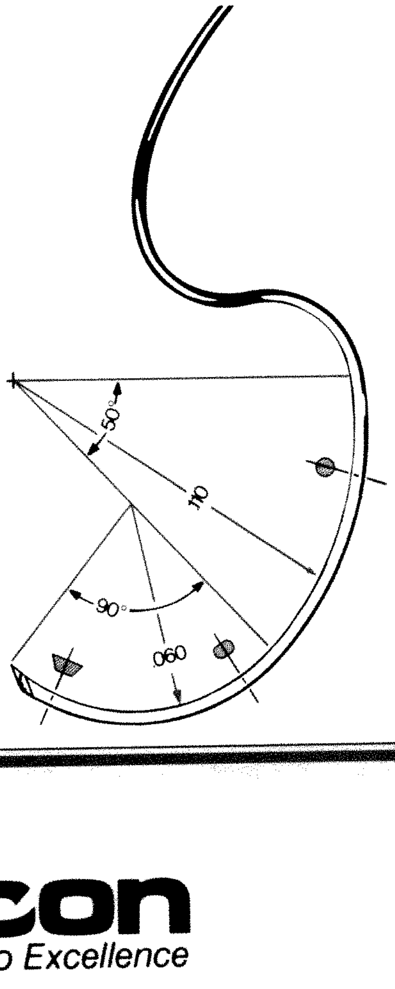

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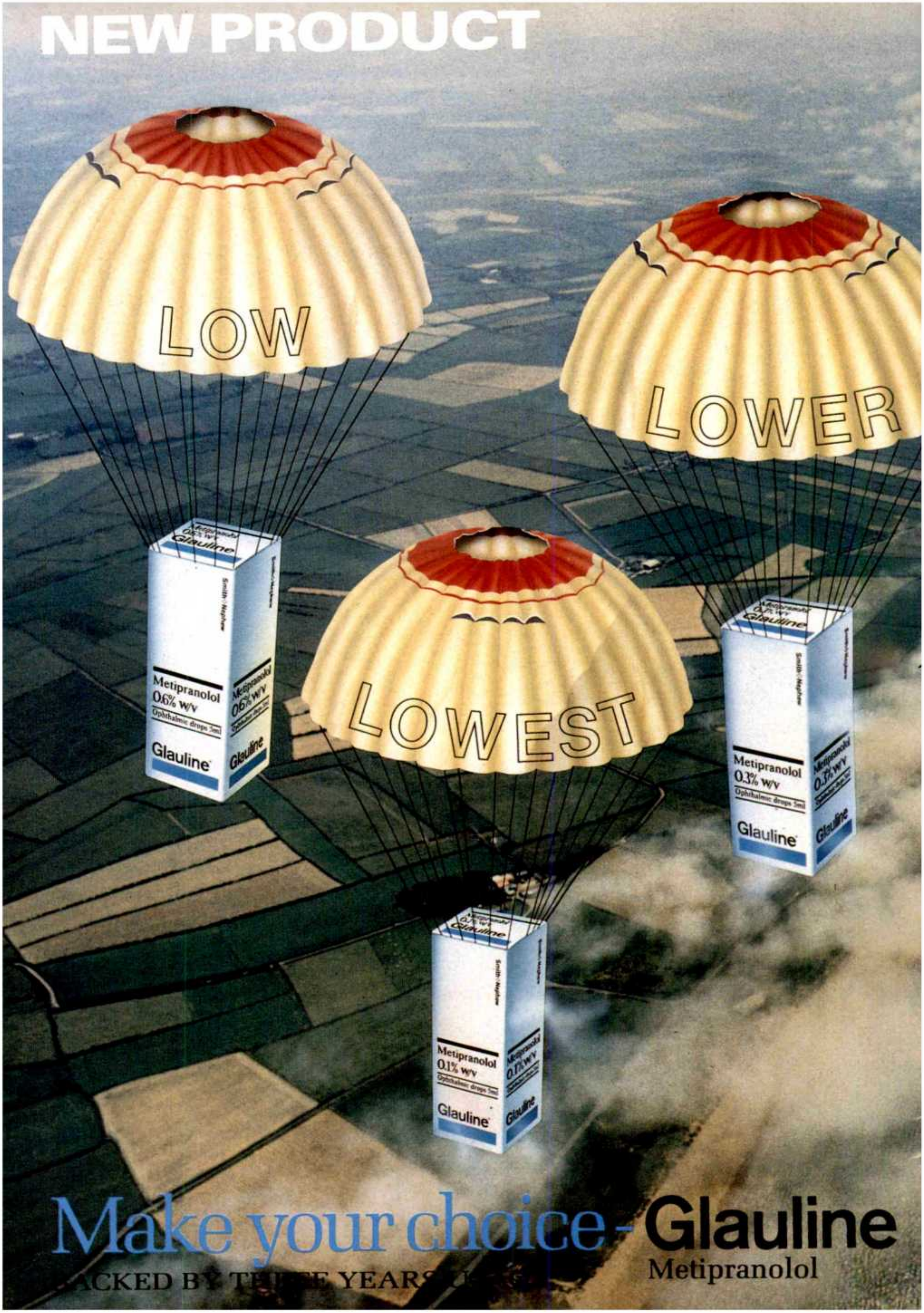
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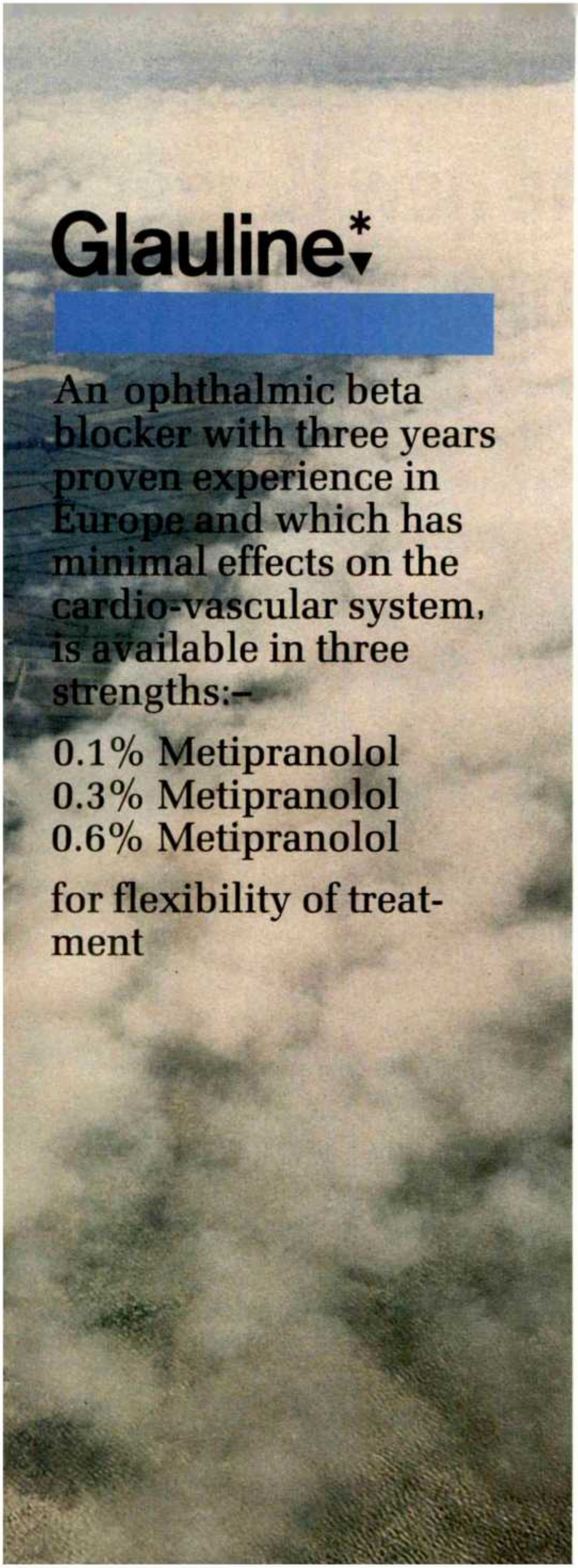

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British Journal of Ophthalmology, 1988, **72**, 55–61

Nocardial endophthalmitis: report of two cases studied histopathologically

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SUMMARY We report two cases of nocardial endophthalmitis. Case 1 is a 66-year-old man whose left eye was enucleated about one month after onset of decreased vision. Ophthalmoscopic examination disclosed multiple choroidal masses. Six weeks before the onset of ocular manifestations he had undergone a prolonged carotid endarterectomy with intraoperative complications. The source of the ocular infection was probably exogenous. Case 2 is a 49-year-old woman who had systemic sclerosis (scleroderma) with severe pulmonary insufficiency. She had received moderate doses of corticosteroids. Seventeen months after initiation of therapy she developed ocular manifestations leading to enucleation of the eye one month later. Histopathologically, the enucleated eyes in both cases showed numerous branching, Gram-positive, filamentous organisms involving mainly the plane of Bruch's membrane and the subretinal space. The nosological and microbiological aspects of nocardiosis are reviewed.

Although nocardiosis was first described in Europe, all reported cases of nocardial endophthalmitis have appeared in the American literature except for a recently published one from Thailand.[1]

In this paper we describe our experience with two cases of nocardial endophthalmitis.

Case reports

CASE 1

A 66-year-old white man, a resident of Texas, consulted an ophthalmologist on 12 November 1979 because of decreasing vision in his left eye for the preceding two weeks. Corrected visual acuity in the left eye was 20/200. A mild anterior uveitis was present in that eye. On ophthalmoscopic examination 'multiple metastatic tumours of the choroid' were described. A comprehensive examination was undertaken in a search for a primary tumour elsewhere in the body, but the results of these studies were unremarkable except for detection of a 'testicular mass'. The patient was referred to a urologist but meanwhile had developed secondary glaucoma with forward displacement of the lens-iris diaphragm, and the eye was enucleated in December 1979.

On *gross examination* the chamber angle was occluded by peripheral anterior synechias and the lens-iris diaphragm was displaced anteriorly. The lens was cataractous. The vitreous body was yellow and was markedly condensed anteriorly by a funnel-shaped haemorrhagic retinal detachment. The vitreous body was generally cloudy and contained clumps of cellular material. Underlying the detached retina, both nasally and temporally, were several discrete white masses (Fig. 1) some of which arose from the inner aspect of the choroid and elevated the retinal pigment epithelium. The subretinal space contained an extensive exudate that was organised in some areas.

On *microscopic examination* the iris showed neovascularisation, and the chamber angle was occluded on one side by peripheral anterior synechia formation. There was a scattering of neutrophils in the posterior chamber and along the surface of the ciliary processes. The vitreous body contained fibrin and a moderate number of neutrophils. The retina was totally detached; the subretinal space contained a

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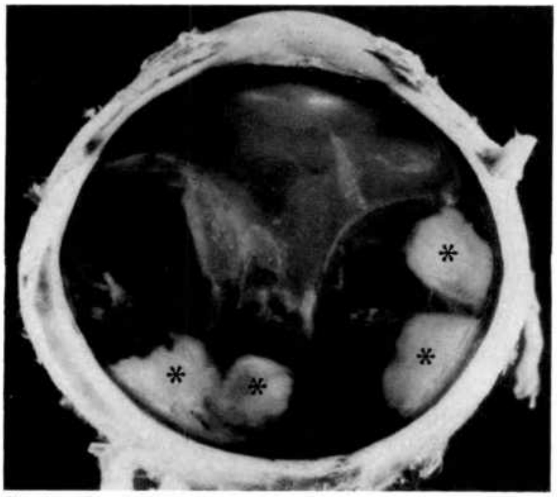

Fig. 1 *Case 1. Gross appearance of one calotte, depicting a bullous retinal detachment. Multiple detachments of the retinal pigment epithelium with greyish white mounds of coagulated proteinaceous exudate (asterisks) are noted.*

purulent exudate and proteinaceous material. There were multiple detachments of the retinal pigment epithelium. In those areas the retinal pigment epithelium was necrotic and was abruptly elevated by large collections of neutrophils and proteinaceous exudate (Fig. 2). The choroid was thickened and oedematous. An extensive infiltrate of neutrophils was located throughout its inner layers. Multiple microabscesses were present along the inner portion of the choroid. The inflammatory infiltrate extended throughout the sclera in some places. The episclera was thickened with areas of granulation tissue, capillary proliferation, and foci of inflammatory cells. Gram stains revealed numerous branching, Gram-positive, filamentous organisms that were located chiefly along the plane of Bruch's membrane and extended into both the subretinal space and the inner portion of the choroid (Fig. 3). The organisms were acid-fast and were morphologically highly characteristic of *Nocardia asteroides*.

On establishment of the diagnosis of nocardial endophthalmitis the patient's past medical history was investigated further. Six weeks before the onset of ocular symptoms he had undergone carotid endarterectomy. The procedure was prolonged, requiring several hours for completion, because of rupture of the posterior wall of the artery. A search was made in an effort to find a primary focus of infection. A bone scan was normal, as were the results of chest roentgenography and intravenous nephrotomography. Urological examination revealed that the epididymis was thickened bilaterally, with globular enlargement of both tails. The masses were distinctly separate from the testes, which appeared normal. The clinical impression was of chronic epididymitis. The prostate gland was described as being slightly lumpy but otherwise unremarkable. A resection of the enlarged right epididymis was performed. Histopathological examination disclosed a chronic epididymitis of undetermined cause. Further follow-up studies four months after enucleation of the eye disclosed no evidence of localised or disseminated nocardiosis.

CASE 2

In February 1983 a 49-year-old white woman consulted a physician because of increasing dyspnoea on

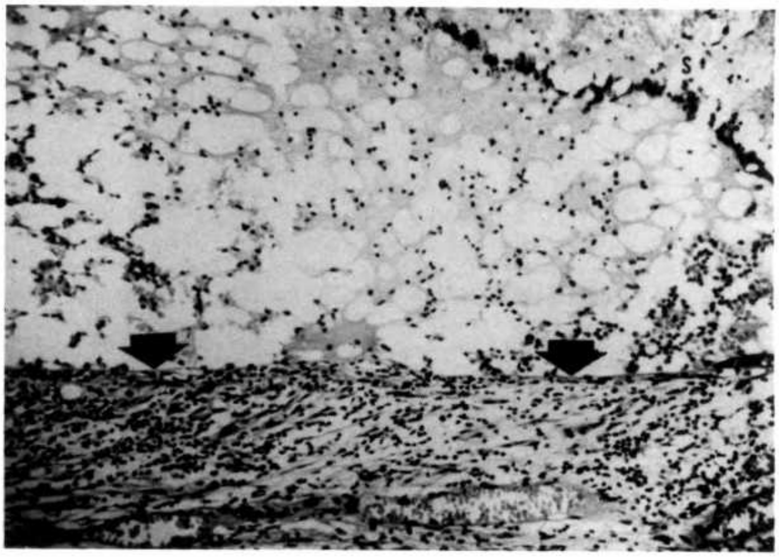

Fig. 2 *Case 1. Proteinaceous exudate containing numerous neutrophils is interposed between the elevated, detached retinal pigment epithelium (upper right corner of field) and the underlying intact Bruch's membrane (arrowheads). The choroid displays a diffuse lymphocytic infiltrate.* S: *Subretinal space. Haematoxylin and eosin.*

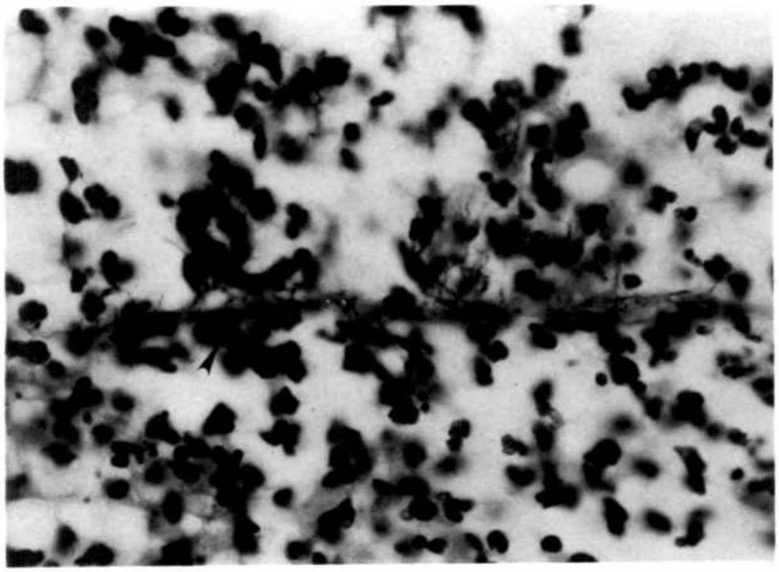

Fig. 3 *Case 1. Many branching, Gram-positive, filamentous organisms are observed on Bruch's membrane. Some of them extend superiorly into the subretinal space. Only a few organisms (arrowhead) are observed in the inner choroid. The latter contains a prominent neutrophilic infiltrate. Brown and Hopps stain.*

exertion and a non-productive cough of one year's duration. The patient, who lived in Virginia, had no previous history of pulmonary disease. Chest roentgenograms showed 'diffuse interstitial disease', and physiological testing disclosed considerable reduction of pulmonary function. A biopsy specimen of the lung was obtained at the time of bronchoscopy and demonstrated 'significant increase in fibrous tissue, with some lymphocytes and plasma cells present.' Treatment with prednisone (40 mg per day) was begun in April 1983. This afforded moderate symptomatic improvement over the next few months, but the results of pulmonary function testing did not show objective improvement. By the latter part of 1983 the prednisone had been reduced to 30 mg every other day.

In May 1984 the patient complained of increased dyspnoea on exertion and difficulty in swallowing solid food. Chest roentgenograms showed no change from those seen previously, but pulmonary function tests demonstrated a marked further decline in function. Investigation of her dysphagia included an upper gastrointestinal radiographic series, which showed abnormal oesophageal motility characteristic of that seen in systemic sclerosis (scleroderma). The patient also had tightening of her skin, which appeared glossy. A diagnosis of systemic sclerosis was made on the basis of the dermatological and gastrointestinal findings.

Her prednisone dose was increased to 60 mg per day because of her deteriorating pulmonary status. In September 1984 she was found to have a compression fracture of her seventh thoracic vertebra. At that time she also reported progressive decrease in visual acuity of her left eye, which she had first noted two months previously, and she was referred for ophthalmic examination. Associated symptoms and signs included redness, pain, and photophobia of the left eye. Visual acuity in her asymptomatic right eye was correctable to 20/25. The right eye was normal on detailed ophthalmic examination. With the left eye the patient was unable to perceive light. The left upper and lower eyelids were mildly swollen. The conjunctiva showed chemosis and prominent vascular injection. The left cornea was clear. The anterior chamber showed 3+ flare and cells. The pupil responded to light only consensually. Intraocular pressure was equivalent to 18 mmHg. The vitreous body contained a prominent exudate of cells and protein. Ophthalmoscopic examination disclosed extensive choroidal infiltration, with elevation of the optic nerve head. Multifocal, yellow-white, subretinal nodules were observed. There was an extensive retinal detachment.

Sinus roentgenograms, blood cultures, and a lumbar puncture were normal. B-mode ultrasonography demonstrated a 'total retinal detachment', with solid, homogeneous 'inflammation' of the choroid. Computerised tomography of the intracranial cavity gave a normal picture.

The eye was enucleated on 5 October 1984. We opened the unfixed eye to obtain material for microbiological examination. There was extensive detachment of the retina. The most striking abnormality was the presence of large, yellowish white nodular masses in the subretinal space (Fig. 4). There were scattered, small, retinal and subretinal haemorrhages. The vitreous body was only mildly opacified.

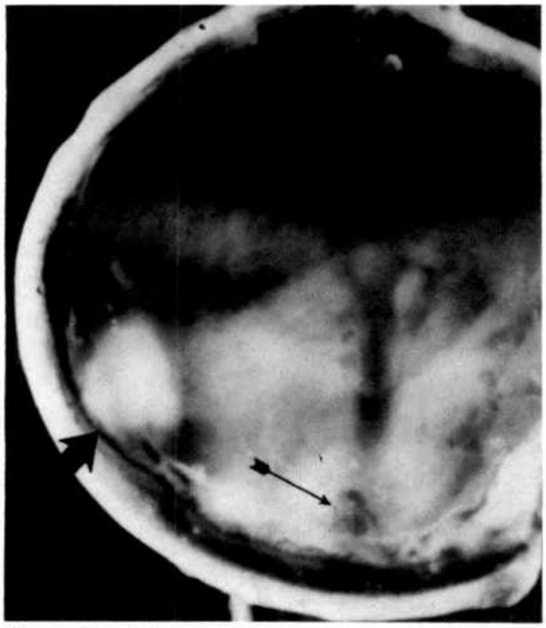

Fig. 4 *Case 2. Large, yellowish white abscesses are present in the subretinal space. The one on the left (heavy arrow) has a nodular configuration. Farther centrally in the field the subretinal abscess formation is more diffuse. There are scattered retinal haemorrhages, one of which is indicated with the fine arrow.*

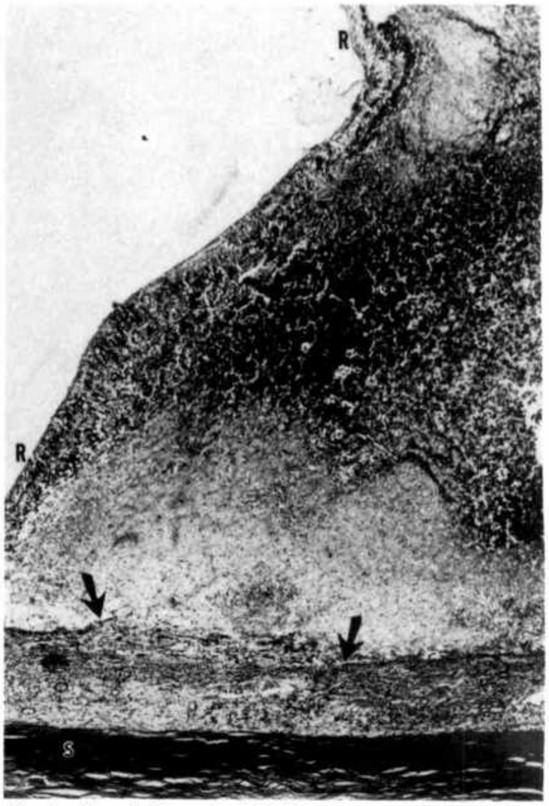

Fig. 5 *Case 2. The retina* (R) *is barely recognisable and is markedly elevated by a suppurative mass in the subretinal space. The choroid is thickened. The retinal pigment epithelium and Bruch's membrane are intact on the right and left sides of the field. But centrally (between the arrows) these structures have been destroyed, permitting confluence of the choroidal inflammatory process with the subretinal abscess.* S: *Sclera. Haematoxylin and eosin.*

On *microscopic examination* the anterior chamber contained a scanty fibrinous exudate, immersed in which were occasional inflammatory cells, chiefly neutrophils. Extensive, narrow, peripheral anterior synechias were present. There was a slight to moderate inflammatory cell infiltrate in the iris, but the ciliary body contained only a light sprinkling of inflammatory cells. The vitreous body contained a mild proteinaceous exudate and a mild to moderate scattered infiltrate of inflammatory cells, chiefly neutrophils. The most striking findings were in the posterior segment. The retina was extensively detached. Where it did remain in place it was sealed by dense scars to the underlying choroid. Throughout much of its extent posteriorly the retina was barely recognisable and was markedly elevated by a suppurative inflammatory mass (Fig. 5) in which neutrophils predominated.

The choroid was diffusely thickened. Particularly in the outer layers of the choroid the inflammatory cell infiltrate consisted chiefly of lymphocytes, plasma cells, and plasmacytoid cells. In the inner portion of the choroid neutrophils were considerably more numerous, and focal areas of the choriocapillaris exhibited abscess formation. In some planes of section the inflammatory features were granulomatous in nature, with many epithelioid cells and giant cells being present, particularly in the inner layers of the choroid (Fig. 6).

Although Bruch's membrane remained intact throughout most of the eye, there were focal areas in which this structure was destroyed, permitting confluence of the inflammatory masses in the choroid and subretinal space (Fig. 5). A Brown-Brenn stain demonstrated Gram-positive, delicate filaments, no more than 1 μm in diameter, which showed prominent branching at right angles.

The organisms were most abundant in the subretinal necrotic inflammatory exudate. None were present in the vitreous body or in the choroid, though organisms were identified within the retinal pigment epithelium, for which they appeared to have a certain avidity. The bacteria were not stained by haematoxylin and eosin, or by the periodic acid Schiff-

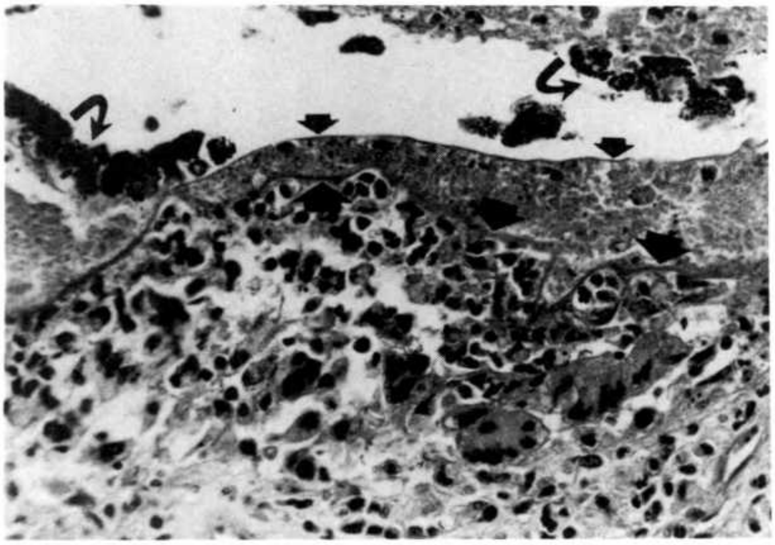

Fig. 6 *Case 2. Bruch's membrane (arrowheads) is split, the two layers being separated by purulent debris. Curved arrows indicate retinal pigment epithelium, which in the upper right part of the field is necrotic and adjoins the abscess in the subretinal space. The innermost layers of the choroid contain a prominent infiltrate of inflammatory cells, most conspicuous of which are several large giant cells on the right side of the field. Haematoxylin and eosin.*

haematoxylin (PAS-H) stain. The Gomori methenamine silver (GMS) stain demonstrated them readily (Fig. 7A), considerably better than did the Brown-Brenn stain. The organisms were also demonstrated extremely well with the van Orden stain (Fig. 7B), and stained weakly with the acid fast technique.

On the basis of these histopathological observations we made a diagnosis of nocardiosis. Several days later we received word from the microbiology laboratory that *Nocardia asteroides* was beginning to grow from material we had obtained from the inflammatory intraocular mass at the time of gross examination.

After we established the diagnosis of nocardiosis the patient's dose of prednisone was tapered to 10 mg every other day. A long-term course of treatment with oral sulphonamides was begun immediately. We borrowed the paraffin block containing lung tissue that had been obtained at the time of bronchoscopy in 1983. In the small tissue sample we found no evidence for systemic sclerosis. Special stains failed to demonstrate any organisms. Follow-up examination in April 1986 disclosed that the patient's health had improved markedly. She had gained 10 lb (4·5 kg) in weight and was feeling much stronger. Pulmonary function studies gave unchanged results, and her right eye showed no change.

Discussion

Nocardiosis is typically caused by *Nocardia asteroides*.[2] The organism is named for the star-like appearance of the colonies on agar and for Edmond Nocard, a French bacteriologist and veterinary pathologist. He isolated a filamentous organism from bovine farcy and in 1889 the name *Nocardia farcinica* was given to it.[2] Bovine farcy is now known to be caused by an unusual strain of mycobacterium that resembles nocardia.[2] It is not known whether the organism originally isolated by Nocard was *Mycobacterium farcinogenes* or what is now classified as *Nocardia asteroides*. The latter was finally identified in 1896 by Blanchard from an organism that Eppinger had called *Cladothrix asteroides* after he isolated it in 1891 from the brain abscess of a patient with systemic nocardiosis.[2]

Nocardia asteroides was formerly thought to be a fungus but is now classified as a bacterium. The organisms are soil borne. They are natural soil saprophytes and are often found in decaying organic matter, such as wet hay or straw. Filamentous branching cells (Fig. 7A) occur during logarithmic phase growth, but these later fragment to small coccobacillary forms (Fig. 7B).[3] The delicate, filamentous organisms are rarely more than 1 μm in diameter and show prominent right-angle branching. The bacteria are diffusely distributed in the purulent exudate of the lesions, thus differing from the filaments of *Actinomyces israelii*, which form granules.[4] *Nocardia asteroides* is not stained by haematoxylin and eosin or by Schiff's periodic acid technique. The organisms are well demonstrated by Gram stains (they are Gram-positive) and by the Gomori methenamine silver stain, provided the time in the silver nitrate solution is increased by about 50%.[3] *Nocardia asteroides* is partially, and weakly, acid-fast by the Ziehl-Neelsen method. Acid-fast stains (particularly the Cross modification to prevent exces-

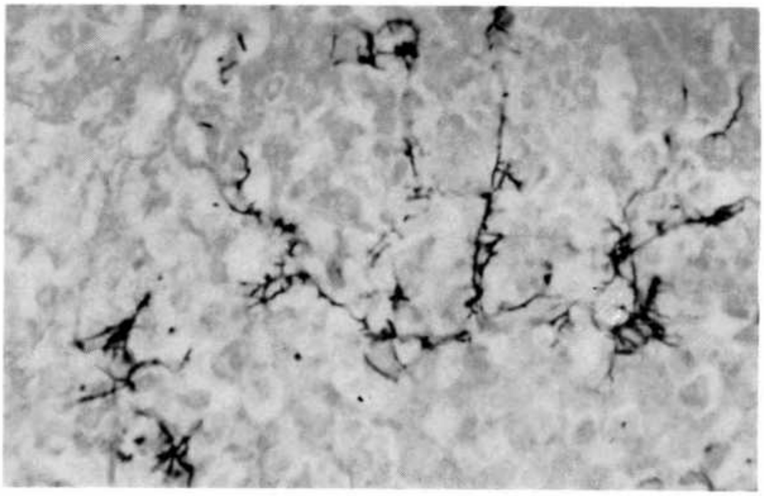

Fig. 7A *Case 2. Branching filamentous organisms in the subretinal abscess. Gomori methenamine silver.*

sive decolorisation) will clearly demonstrate the organism, but its tendency to fragment into coccobacillary forms may cause it to be confused with *Mycobacterium tuberculosis* or atypical mycobacteria.[14] The van Orden stain demonstrates the organisms extremely well (Fig. 7B).

The organisms are not fastidious in culture, but they tend to grow slowly. They will grow on virtually any bacterial, fungal, or mycobacterial medium that lacks antibiotics, and will grow within a wide temperature range. Growth of *Nocardia asteroides* is facilitated by 10% carbon dioxide. In pure culture the colonies often grow out after only 48 hours of incubation, but in mixed culture or in primary isolation from clinical material the colonies can take as long as two to four weeks to appear.[2] Unless the organism is suspected, its recognition poses a practical problem, because culture plates tend to be overgrown by microbial contaminants (especially in sputum) and are often discarded after 48 hours, whereas *Nocardia asteroides* may require considerably longer for growth. As a result, the organism is more likely to be identified on media used for mycobacteria or fungi, which are observed for longer periods.[3] In our second case we made the diagnosis of nocardiosis by examining tissue sections before the organism appeared on culture media in the microbiology laboratory.

Nocardiosis is presumed to result from inhalation of airborne bacteria. There is no evidence for spread from infected persons or animals. Although the disease can occur in apparently normal people, it is

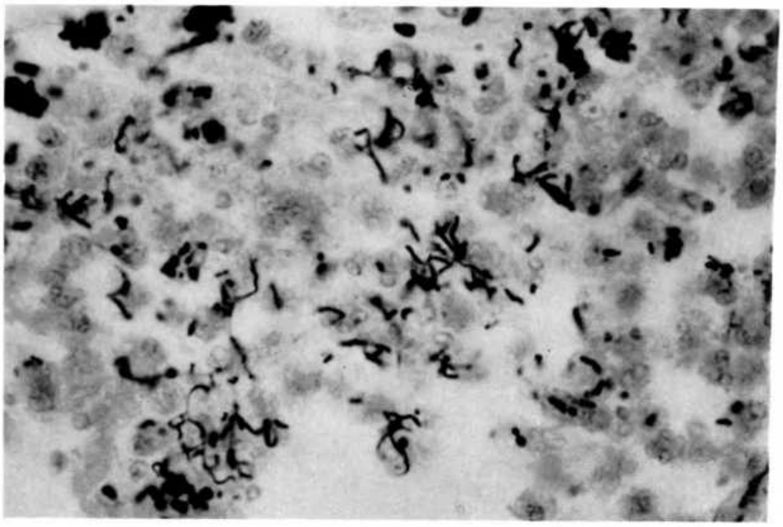

Fig. 7B *Case 2. In another area of the eye the bacteria have forsaken their filamentous growth pattern and have fragmented into small coccobacillary forms. van Orden stain.*

encountered much more commonly in immunosuppressed patients.[2] Nocardiosis appears as a pneumonic process in about 75% of cases. In 25 to 40% of patients there is dissemination to the central nervous system. Other common sites of dissemination include the skin and subcutaneous tissues, pleura and chest wall, kidney, liver, and lymph nodes.[3]

A total of 11 cases[2,5–12] of *endogenous* nocardial endophthalmitis has been reported in the literature. Each of these reports concerns a single patient except the articles by Bullock[2] and by Meyer and coworkers,[6] in both of which two cases of endogenous nocardial endophthalmitis were described. Pathological examination of the eye was carried out in all 11 of these patients except for one of the two patients reported on by Bullock. An unpublished case of endogenous nocardial endophthalmitis (from Chicago) was presented by Robert Levine at the 1979 meeting of the Armed Forces Institute of Pathology Ophthalmic Alumni.[13] All these reports of endogenous nocardial endophthalmitis appeared in the American ophthalmic literature and we are unaware of any such cases that may have been presented at ophthalmic pathology society meetings outside the United States.

Five reports[1,6,14–16] (each involving a single case) of *exogenous* nocardial endophthalmitis following either accidental or surgical penetrating wounds of the eye have been published.

Common features in the other cases of nocardial endophthalmitis that have been examined pathologically are the suppurative and necrotising nature of the inflammatory response in the inner layers of the choroid and in the retina, and the presence of subretinal abscesses. In only one of the reported cases has the inflammatory response assumed a granulomatous quality in some areas.[10] As in our second case, the epithelioid cells and giant cells were most prominent in the inner layers of the choroid and immediately adjacent thereto, in the region of the retinal pigment epithelium and Bruch's membrane.[10] In both of the cases we are reporting the organisms showed a remarkable tendency to grow along Bruch's membrane and seemed to have a peculiar affinity for the retinal pigment epithelium. On reviewing the previously published cases in this regard we find some of them too sparing in detail to permit evaluation of this point. But in at least five of the previously described cases[6,9–12] the authors mentioned the prominent growth of the organisms along Bruch's membrane, often associated with detachments of the retinal pigment epithelium.

Nocardiosis is a systemic disease for which sulphonamides are the treatment of choice. The duration of therapy is poorly standardised, but should be prolonged because relapse is common. In patients with intact host defences treatment should be continued for at least six weeks following clinical recovery. In immunosuppressed patients therapy should be given for at least one year.[3] Reducing the dose, as the clinical situation permits, of any immunosuppressive drugs the patient may be taking is a keystone of management.

This study was supported in part by grants from Research to Prevent Blindness, Inc (Dr Ferry), and from the Retina Research Foundation and the Lions Eye Bank, Houston (Dr Font).

References

1 Chiemchaisri YW, Imwidthaya S, Parichatikanond P. Exogenous intraocular nocardiosis. *J Med Assoc Thailand* 1985; **68:** 29–32.

2 Bullock JD. Endogenous ocular nocardiosis: a clinical and experimental study. *Trans Am Ophthalmol Soc* 1983; **81:** 451–531.

3 Drutz DJ. Nocardiosis. In: Wyngaarden JB, Smith LH, eds. *Cecil's textbook of medicine.* 17th ed. Philadelphia: Saunders, 1985: 1613.

4 Binford CH, Dooley JR. Nocardiosis. In: Binford CH, Connor DH, eds. *Pathology of tropical and extraordinary diseases.* Washington, DC: Armed Forces Institute of Pathology, 1976: 555.

5 Davidson S, Foerster HC. Intraocular nocardial abscess, endogenous. *Ophthalmology* 1967; **71:** 847–50.

6 Meyer SL, Font RL, Shaver RP. Intraocular nocardiosis: report of three cases. *Arch Ophthalmol* 1970; **83:** 536–41.

7 Burpee JC, Starke WR. Bilateral metastatic intraocular nocardiosis. *Arch Ophthalmol* 1971; **86:** 666–9.

8 Panijayanond P, Olsson CA, Spivack ML, *et al.* Intraocular nocardiosis in a renal transplant patient. *Arch Surg* 1972; **104:** 845–7.

9 Jampol LM, Strauch BS, Albert DM. Intraocular nocardiosis. *Am J Ophthalmol* 1973; **76:** 568–73.

10 Rogers SJ, Johnson BL. Endogenous *Nocardia* endophthalmitis: report of a case in a patient treated for lymphocytic lymphoma. *Ann Ophthalmol* 1977; **9:** 1123–31.

11 Sher NA, Hill CW, Eifrig DE. Bilateral intraocular *Nocardia asteroides* infection. *Arch Ophthalmol* 1977; **95:** 1415–8.

12 Lissner GS, O'Grady R, Choromokos E. Endogenous intraocular *Nocardia asteroides* in Hodgkin's disease. *Am J Ophthalmol* 1978; **86:** 388–94.

13 Levine RA. Nocardial endophthalmitis. Presented at the Eighth Biennial Meeting of the Armed Forces Institute of Pathology Ophthalmic Alumni. Washington, DC, 22–3 June 1979.

14 Batshon BA, Brosius OC, Snyder JC. A case report of Nocardia asteroides of the eye. *Mycologia* 1971; **63:** 459–61.

15 Lass JH, Thoft RA, Bellows AR, Slansky HH. Exogenous *Nocardia asteroides* endophthalmitis associated with malignant glaucoma. *Ann Ophthalmol* 1981; **13:** 317–21.

16 Chen CJ. *Nocardia asteroides* endophthalmitis. *Ophthalmic Surg* 1983; **14:** 502–5.

Accepted for publication 21 November 1986.

British Journal of Ophthalmology, 1988, **72**, 62–64

Norrie's disease in an Asian family

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SUMMARY Norrie's disease, a congenital progressive oculo-acoustico-cerebral degenerative condition, is a sex linked recessive disorder. Previously described as atrophia oculi congeneti, it is associated with bilateral pseudotumour of the retina, lens, and corneal opacities, and phthisis bulbi. Some patients develop progressive deterioration of mental function and hearing. We report a Sri Lankan family with typical features of Norrie's disease.

Norrie,[1] a Danish ophthalmologist, surveyed the causes of blindness in Danish institutes for the blind, and described a congenital type of blindness as atrophia oculi congeniti. It affected only males and occurred in several generations. Warburg[2] subsequently reviewed the data available and suggested the name Norrie's diseases for congenital bilateral pseudotumour of the retina, of sex linked recessive inheritance, with complete penetrance but varied expressivity. Mental deficiency occurs in about a third of the patients, and 25%–30% develop a progressive neural hearing loss.[3] The ocular lesion produces lens and corneal opacities and subsequently phthisis bulbi.[2]

Most of the reports of Norrie's disease are from Denmark and Sweden.[3] But subsequently reports from Australia, the Netherlands,[4] and the United States[5,6] have been published. The first report from the United States was in a Negro family.[5] A similar condition has been described among Greek Cypriots[7] and Canadian Indians,[8] which from genetic, clinical, and histopathological studies closely resemble Norrie's disease.[9] Warburg[3] interpreted many other cases reported from England, Germany, Austria, Spain, Switzerland, and Cuba as Norrie's disease. There are no reports of this condition in Sri Lankans, and to our knowledge it has not been reported in Asians.

Case reports

CASE 1

A 3-year-old boy presented with a history of blindness from birth and delayed milestones. He was delivered normally at term, and the postnatal period was normal. The mother's antenatal period was uneventful. The mother noticed during early infancy that he did not respond to light and appeared blind. His milestones were delayed in comparison with his elder sister's. At the age of 3 years he could roll over and grasp objects when handed over, and he could sit without help. Though his hearing appeared to be normal, he could not speak single words. He was also in the habit of head banging. On examination of the eyes, he had an irregular pupil on the right side, bound by synechiae. A central cataract was seen, the pupil was occluded by a yellowish grey mass, and the fundus could not be visualised. An extensive corneal opacity of the left eye was observed, and the globe was soft and phthisical.

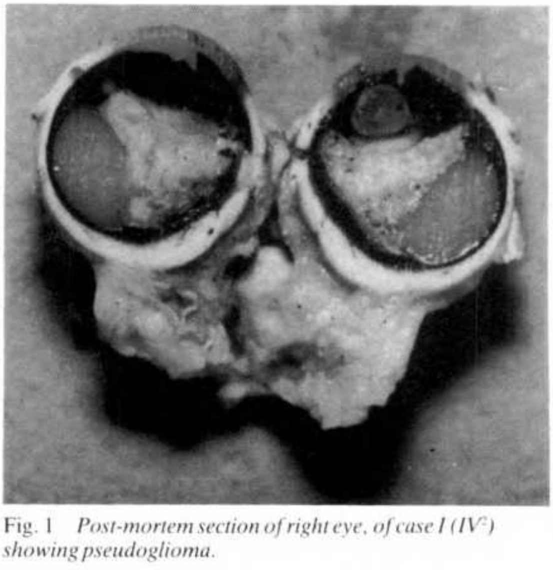

Fig. 1 *Post-mortem section of right eye, of case 1 (IV^2) showing pseudoglioma.*

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At the age of 4 years the child died suddenly after an episode of vomiting and drowsiness. Histological examination of the right eye (Fig. 1) showed fibrovascular granulation tissue behind the lens, in which many areas were hyalinised, with scar formation. Marked hyperplasia of pigment epithelium and areas of ossification behind the lens were seen. Hypoplasia of the inner layer of the retina, and necrosis with infilteration by lymphocytes, plasma cells, and a few multinucleated giant cells, was observed.

CASE II

The younger sib of case I, this 1-year-old boy also presented with a history of blindness from birth. His milestones were normal and he could sit up without help and speak single words. He had bilateral central cataracts. There was a central corneal leucoma in the right eye. The left cornea was hazy, and the pupil was completely occluded by a proliferative yellowish grey mass. The fundi could not be visualised. He was referred to Colombo for a second opinion, where both cataracts had been removed without any improvement in the sight. At the age of 16 months there was evidence of regression of milestones. Although he could sit up without help at the age of 8 months, he was not able to do so on his own at the age of 16 months, and he made rocking movements of his body back and forth.

FAMILY HISTORY

The pedigree of the family (Fig. 2) was studied extensively. Two of the mother's (III^{14}) brothers (III^{12} and III^{17}) were affected; the elder brother (III^{12}) had been blind from birth and had died of an unknown cause, associated with helminthiasis. The other (III^{17}, aged 27 years) had also been blind from birth. His milestones were normal, and had been an inmate of the Rathmalana Blind School. In recent years he gradually became withdrawn and psychotic in his behaviour. His hearing is apparently normal. The maternal grandmother (II^{11}) had four brothers (II^{3}, II^{6}, II^{9}, II^{10}) who were blind from birth. One (II^{6}) had died during childhood of an unknown cause; the others had been to the Blind School, and the relatives did not know where they are now. The grandmother's (II^{11}) eldest sister's (II^{2}) one son (III^{4}) was also affected. He had initially been diagnosed as having bilateral malignant tumours, probably retinoblastoma, and both eyes had been enucleated during childhood. After surgery the parents had been informed that it was not a malignant condition. He is now partially deaf, but not retarded. The grandmother's (II^{11}) younger sister (II^{13}) too has had two male children who were blind. Both of them died during childhood, one (III^{22}) being drowned in a well and the other (III^{28}) dying of an illness associated with helminthiasis.

Discussion

The study of the pedigree in four generations strongly suggests a sex linked recessive disorder, which makes acquired conditions very unlikely.

The evidence of sex linked inheritance, blindness

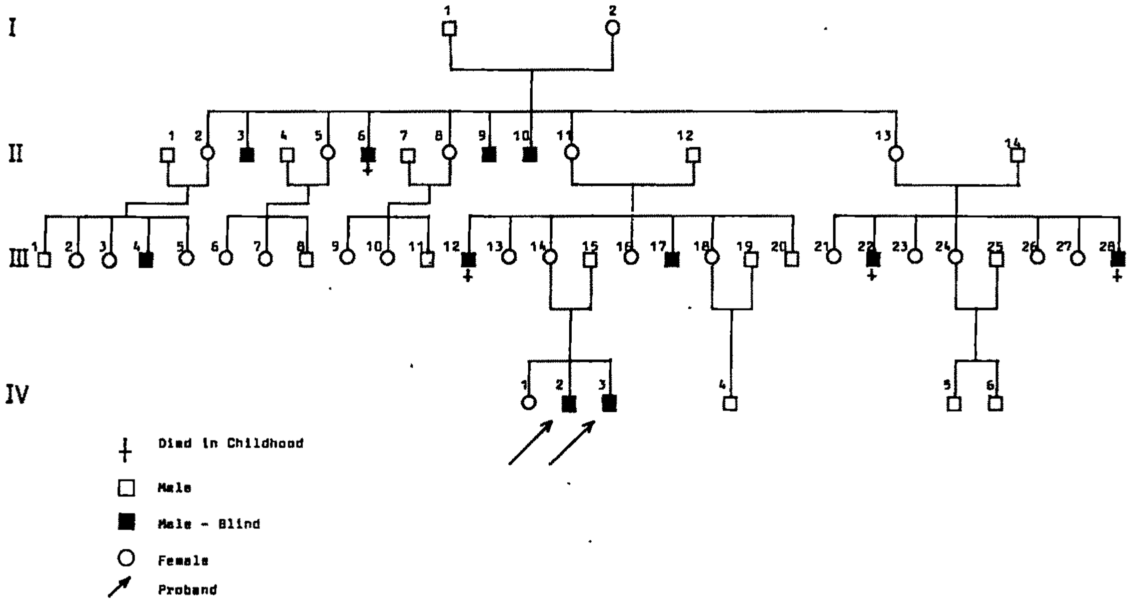

Fig. 2 *Family pedigree.*

from birth, mental retardation, and the characteristic ocular changes of bilateral pseudotumour, cataracts, corneal degenerative changes, phthisis bulbi, and associated deafness in one family member, justify the diagnosis of Norrie's disease in this family. The histological appearance of the eye in case I is also consistent with those described in Norrie's disease.[3]

It is of interest to note that one of the family members (III^{4}) had his eye enucleated for suspected malignancy. Warburg's first case[3] also underwent enucleation for suspected retinoblastoma. Of the 16 families traced in the literature enucleation has been performed in three patients.[3]

Warburg[3] suggests that the disease causes degenerative changes in the retina, sometimes in the cerebrum and in the acoustic nerves. This could account for the progressive withdrawal and psychotic behaviour in one member of this family (III^{17}), and mental retardation and early regression in our two patients. Strikingly similar regressive mental changes have been observed by Hansen[5] and Holmes.[6] Hansen[5] describes rocking movements back and forth made by his patient. Warburg[3] also mentions similar movements in one patient (family BJ—IV^{10}). One of our patients (IV^{3}) behaved in a similar manner. Self mutilation was observed by Warburg[3] in some of the patients studied; one of our patients (IV^{2}) was in the habit of banging his head.

Blindness, especially if associated with mental retardation, increases the risk of fatal accidents in early childhood. An example of this was seen in patient III, who had drowned in a well. A child belonging to a family in Warburg's series[3] had also drowned in a well.

A striking feature in the pedigree is that many of the females in the third generation are not married. On questioning the mother (III^{14}) it was apparent that the female relatives of the mother are well aware of the nature of the disease and its inheritance. They are therefore reluctant to get married. It is of interest to note that both these children were referred to the first author (DGH de S) by an obstetrician, when the mother (III^{14}) had insisted on permanent sterilisation in spite of having only one normal girl. In contrast, Warburg[3] stressed the need for urgent eugenic counselling in the families studied by her, because very few were aware of the risk factors.

We wish to thank Prof Asoka de S Gunasekara, for referring these two patients, medical student S Gamage for help in tracing the family pedigree, Dr P U Thelisinghe for histological studies and Mr P B Y de Silva for typing the manuscript.

References

1 Norrie G. Causes of blindness in children. *Acta Ophthalmol (Kbh)* 1927; 5: 357.
2 Warburg M. Norrie's disease. A new hereditary bilateral pseudotumour of the retina. *Acta Ophthalmol (Kbh)* 1961; 39: 757–72.
3 Warburg M. Norrie's disease. A Congenital progressive oculoacoustico-cerebral degeneration. *Acta Ophthalmol (Kbh)* 1966; 89 (suppl): 1–147.
4 Warburg M. Quoted by Hansen AC.[5]
5 Hansen AC. Norrie's disease. *Am J Ophthalmol* 1968; 66: 328–32.
6 Holmes LB. Norrie's disease—an X-linked syndrome of retinal malformation, mental retardation and deafness. *N Engl J Med* 1971; 284: 367–8.
7 Taylor PJ, Coates T, Newhouse ML. Episkopi blindness. Hereditary blindness in a Greek Cypriot family. *Br J Ophthalmol* 1959; 43: 340–4.
8 Wilson WMG. Congenital blindness (pseudoglioma) occurring as a sex linked developmental anomaly. *Can Med Assoc J* 1949; 60: 580–4.
9 Anderson SR, Warburg M. Norrie's disease. Congenital bilateral pseudotumour of the retina with recessive X-chromosomal inheritance. Preliminary report. *Arch Ophthalmol* 1961; 66: 614–8.

Accepted for publication 21 November 1986.

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British Journal of Ophthalmology, 1988, **72**, 65–67

Childhood blindness in Jamaica

B J MORIARTY

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SUMMARY Examinations were performed on the 108 blind Jamaican children (VA<6/60 in the better eye) in residential care. The congenital rubella syndrome (CRS) was the leading preventable cause of childhood blindness, accounting for 22% of children examined. Improvement of the rubella immunisation programme and the introduction of appropriate surgical procedures constitute recent attempts to combat childhood blindness.

The causes of childhood blindness in the tropics vary according to climate, nutrition, customs, control of infection, and economic development. The present study describes the causes of blindness in Jamaican children aged 5–15 years and identifies appropriate measures to combat the problem.

Materials and methods

The children examined resided at the Salvation Army School for the Blind in Kingston, where all Jamaican children aged 5–15 years known to have severe visual disability are referred. Unlike many blind schools, this school cares for all 'blind' children, many of whom also suffer from deafness and mental and physical disability. The clinical history and paediatric examination of all children is obtained prior to admission.

All children had an ophthalmic examination in March 1986 by portable slit-lamp microscopy and ophthalmoscopy. Further examination, testing of intraocular pressures, and photography were performed at the Medical Research Council Laboratories and the ophthalmology clinic at the University Hospital of the West Indies. Parents and siblings residing in other parts of the island were traced, whenever possible, to assist in documentation. Further ancillary tests, such as electroretinography, are not available in Jamaica.

Blindness was defined as having visual acuity of less than 6/60 in the better eye despite refractive correction. All the blind children were born in Jamaica and had resided there since birth.

Where possible the causes of blindness were divided into hereditary, prenatal (non-hereditary), perinatal, and postnatal. Hereditary causes were presumptively based on family history, inheritance, and the absence of clinical findings suggestive of prenatal, perinatal, or postnatal disorders.

Results

One hundred and eight blind children (49 males, 59 females) were examined. The commonest causes of blindness (Table 1) were congenital cataract (39%), optic nerve atrophy (18%), and glaucoma (15%). Blindness from the congenital rubella syndrome (CRS) accounted for 24 (22%) of the children and was identified as the leading preventable factor in Jamaica. Blindness in CRS was attributable to

Table 1 *Causes of blindness in 108 Jamaican children aged 5–15 years*

Causes	*Cases* *n (%)*	*Mechanism*
Cataract	=42 (39)	20 Rubella; 14 hereditary; 8 ? cause
Optic nerve atrophy	=19 (18)	6 Hereditary; 5 hydrocephalus; 2 Meningitis; 2 colobomata; 2 trauma; 1 Down's, 1 craniostenosis
Glaucoma	=16 (15)	10 ? Cause; 4 rubella; 2 aniridia
Retina	= 9 (8)	7 Retinitis pigmentosa; 2 retinoblastoma
Myopia	= 7 (6)	5 Hereditary; 2 spontaneous
Uveitis	= 5 (5)	4 Toxoplasmosis; 1 sarcoid
Cornea	= 5 (5)	3 Dystrophy; 2 interstitial keratitis
Maculopathy	= 2 (2)	2 Hypoplasia
Nanophthalmos	= 1 (1)	
Marfan's syndrome	= 1 (1)	
Peters' anomaly	= 1 (1)	
Total	108	

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Table 2 *Causes of childhood blindness in Jamaica and the UK by hereditary and acquired factors*

		Jamaica	*United Kingdom**
Hereditary	=42	(48%)	(50%)
Acquired			
1. Prenatal	=36	(41%)	(6%)
2. Perinatal	= 0	(0%)	(33%)
3. Postnatal	=10	(11%)	(11%)
Total	88		

*Data taken from Fraser and Friedman.[1]

cataract in 20 cases (8 cases with microphthalmos) and glaucoma in four cases.

In 88 children it was possible to classify causes into hereditary and acquired (pre-, peri-, and postnatal), but in 20 children this division could not be applied with complete confidence (10 with glaucoma, six cataract, two retinoblastoma, two myopia). Comparison of these causes with those identified in the UK (Table 2) indicates an absence of perinatal factors.

Discussion

The causes of blindness in the 108 Jamaican children invite comparison with similar studies in the tropics —Saudi Arabia (187 cases),[2] Cyprus (112 cases),[3] Lebanon (231 cases),[4] and Nigeria (140 cases).[5]

The Jamaican picture is characterised by a high prevalence of blindness from CRS, unlike Cyprus, Lebanon, Saudi Arabia, and Nigeria, where rubella is thought to be contracted at a pre-childbearing age. Jamaica, like the UK, is 'modern' in that girls may encounter the virus later in life. However, the Jamaican approach to prevention of CRS is by selective vaccination of girls at 10 or 11 years, with many parishes achieving only 60–70% uptake in the target group.[6] An epidemic of rubella is predicted in Jamaica between 1987 and 1990,[6] and a committee of paediatricians, community health workers and ophthalmologists is promoting public awareness of the vaccine. Vaccination of Jamaican children against diphtheria, pertussis, tetanus, and measles is relatively complete, since failure may delay entry to primary school. Plans to use a combined measles and rubella vaccine at age 1–5 years will reduce disease frequency and generate a population or herd immunity effect.[6]

Cataracts were responsible for blindness in 39% of the children, with CRS the commonest cause. Four children were still resident in the blind school after operation and normal funduscopy, indicating the poor prognosis for delayed operations and deprivation amblyopia. A further two children were found to require discission of an opacified posterior capsule.

Congenital and infantile glaucoma requires earlier detection and surgical intervention than is currently practised. Thermal sclerostomy and goniotomy will hopefully yield favourable results.

Malnutrition and postnatal infection appear to cause little corneal blindness in Jamaica, unlike Saudi Arabia and Nigeria, where keratitis from trachoma and measles prevail. However, the recent economic climate of Jamaica has been characterised by increasing poverty, unemployment, and rising food prices. Hospitalisation for malnutrition and vitamin A deficiency is increasing, and cases of xerophthalmia are reappearing for the first time in over 10 years. Corneal transplantation has not been readily available in Jamaica owing to the absence of necessary instruments and eye-banking facilities. However, recently donated equipment has allowed successful corneal transplantation in three of these children since March 1986. An eye bank is now being established to serve the community.

Hereditary disease accounted for 48% of childhood blindness in Jamaica, similar to the 50% observed in the UK[1] but less than the 77% in Lebanon[4] and 79% in Cyprus.[3] There is little consanguinity in marriage, but the endogamous population in villages may result in autosomal recessive disease. Also it is not uncommon for a Jamaican man to father children from several women; thus it is difficult to establish precise lines of heredity. Some of the 20 cases omitted from classification in Table 2 may in fact be hereditary.

The absence of perinatal causes of blindness (Table 2) contrasts markedly with their occurrence in the UK. This may be attributable to the inadequate facilities and lack of staff trained in ventilation of neonates with respiratory distress syndrome. In the UK these neonates requiring ventilation may survive, though subsequently manifesting retinopathy of prematurity on occasions. This complication will no doubt become manifest with improvement of the facilities for ventilation.

I am indebted to Nurse Helen Patterson (Salvation Army School for the Blind, Kingston) for her assistance with this study. Professor E M Helveston (Department of Paediatric Ophthalmology, Indianapolis), Professor M Dixon (Department of Child Health, UHWI, Kingston), and Professor G R Serjeant (MRC Laboratories, UWI, Kingston) helped by discussion. Mrs S Grant provided secretarial assistance.

The findings described in this paper are to be submitted to the Ministry of Health and the Jamaica Society for the Blind to assist the National Eye Programme Feasibility Study.

References

1 Fraser GR, Friedman AI. *The causes of blindness in childhood. A study of 766 children with severe visual handicaps.* Baltimore: Johns Hopkins Press, 1967: 1–245.
2 Tabbara KF, Badr IA. The changing pattern of childhood blindness in Saudi Arabia. *Br J Ophthalmol* 1985; **69**: 312–5.

3 Merin S, Lapithis AG, Horovitz D, *et al.* Childhood blindness in Cyprus. *Am J Ophthalmol* 1972; **74:** 538–42.
4 Baghdassarian SA, Tabbaro KF. Childhood blindness in Lebanon. *Am J Ophthalmol* 1975; **79:** 827–30.
5 Olurin O. Etiology of blindness in Nigerian children. *Am J Ophthalmol* 1970; **70:** 463–76.
6 Baxter DN. Control of the congenital rubella syndrome in Jamaica. *West Indian Med J* 1986; **35:** 50–4.

Accepted for publication 20 November 1986.

British Journal of Ophthalmology, 1988, **72**, 68–73

Automated morphometry of corneal endothelial cell: use of video camera and video tape recorder

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SUMMARY We developed an apparatus for automated morphometry of the corneal endothelium, which was photographed through a specular microscope connected to a video camera, and the images were stored on a video tape. The clearest stationary image was input into an image analyser to determine automatically the cell boundaries. Although human interaction is generally necessary, the mean time required to complete this procedure was about 13 minutes, based on the results of the 30 normal eyes, and the time needed for manual correction was about 4 minutes. The mean cell area obtained by this method correlated well (r=0·9335) with that obtained by tracing the same images. This apparatus is clinically useful for immediately obtaining the mean cell area of corneal endothelium and will extend the application of specular microscopy to the routine clinical setting.

Morphometry of corneal endothelial cells, which include an analysis of mean cell areas, cell shapes, and cell densities, is now recognised as being indispensable for the evaluation of corneal function in many clinical situations.[1-7] This morphometric analysis is carried out with a digitiser[8-10] or an image analyser.[11,12] In these methods the cell boundaries must be determined by marking the apices of the endothelial cells or by tracing the original photographic image. These tedious and time consuming procedures must be performed manually, increasing the chance of errors. Moreover, since the methods involve photography, there is room for further errors in the enlargement process, and the photographic procedures involved in taking pictures, development, and enlargement require considerable time and labour. To overcome these problems automated techniques of endothelial cell morphometry have been designed by which cell boundaries are determined automatically and directly on the original photograph with an image analyser.[13-17]

We previously reported[17] a method of processing images on 35 mm negative film by inputting them directly into an image analyser for automatic cell boundary determination, and achieved considerable economy of time and energy. However, all attempts at automated morphometry have faced a common problem: the cell images that are commonly obtained in clinical settings are often not distinct enough for completely automated determination of cell boundaries owing to lack of clarity and interference by cell contents such as the nucleus, and they require manual correction. Therefore obtaining clear cell images more frequently and efficiently, making accurate image correction during the analysing process, as well as improving the algorithm of image processing, are critical matters for the routine clinical utilisation of data obtained by endothlial cell morphometry.

From these considerations we developed a more labour and time saving technique employing a video camera (VC) and a video tape recorder (VTR), by which endothelial cell boundaries are automatically determined, and mean cell area as well as cell density are obtained immediately after video-recording.

Material and methods

APPARATUS

A clinical specular microscope (Konansha, CSP580) mounted with a ×50 objective lens was connected to a VC (NEC, TI-22AII), and the images obtained were recorded with a VTR (Sony, U-Matic VO 5800). The clearest images were selected during slow playback, and time base errors were corrected with a digital time base corrector (For-A, FA-400).

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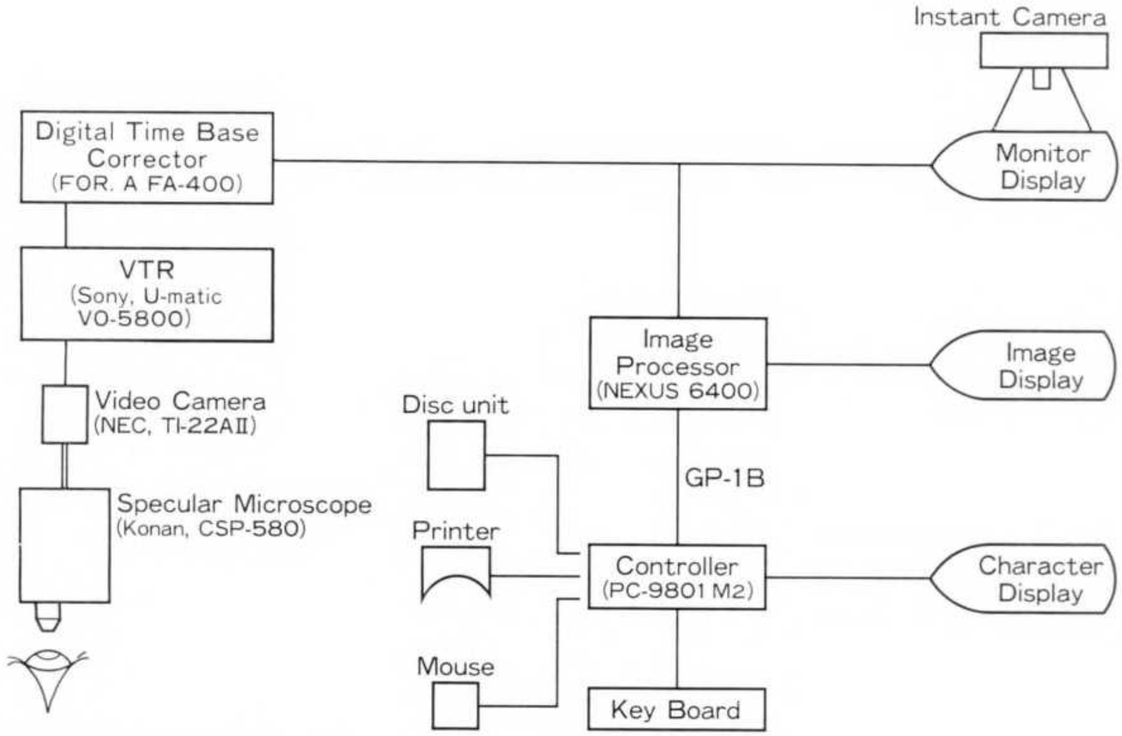
Instant Camera
Digital Time Base Corrector (FOR. A FA-400)
Monitor Display
VTR (Sony, U-matic VO-5800)
Image Processor (NEXUS 6400)
Image Display
Video Camera (NEC, TI-22AII)
Disc unit
GP-1B
Specular Microscope (Konan, CSP-580)
Printer
Controller (PC-9801 M2)
Character Display
Mouse
Key Board

Fig. 1 *Block diagram of the aparatus.*

Stationary images are obtained with its single-frame function, input into an image analyser (NEXUS, 6400), and processed with a microcomputer (NEC, pc-9801M2) (Fig. 1).

ALGORITHM FOR DETERMINATION OF CELL BOUNDARIES

Unprocessed VTR images are input (Fig. 2) and stacked 10–20 times.

Shading compensation of images. High frequency noise is excluded with a 3×3 pixels grid, and differences in brightness among portions of the image are minimised with a 15×15 pixels grid. The compensated images obtained are subtracted from the original image to produce an image in which the cell boundaries are enhanced (Fig. 3).

Binary representation. The enhanced images obtained are converted to binary representation (0 for the dark cell boundary and 1 for the bright cell interior).

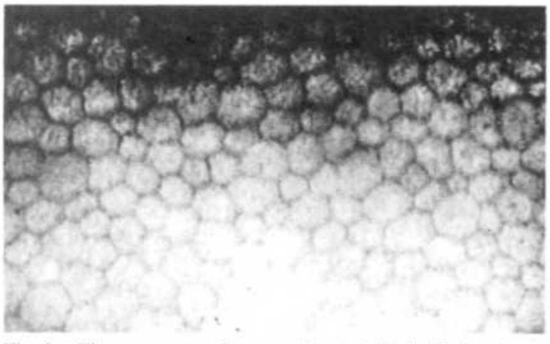

Fig. 2 *The unprocessed image of endothelial cells in a single memory VTR frame.*

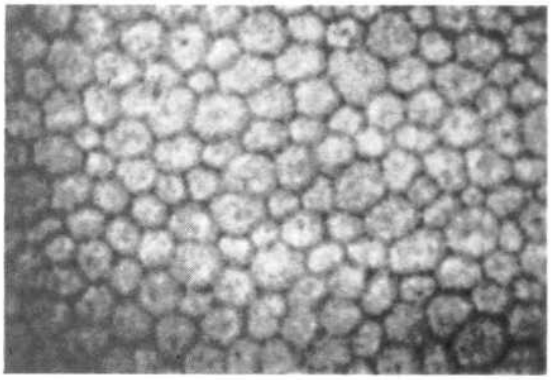

Fig. 3 *Image in which the cell boundaries are enhanced after elimination of high frequency noise, subtraction of the original image from the smoothed image obtained by reducing the difference in brightness.*

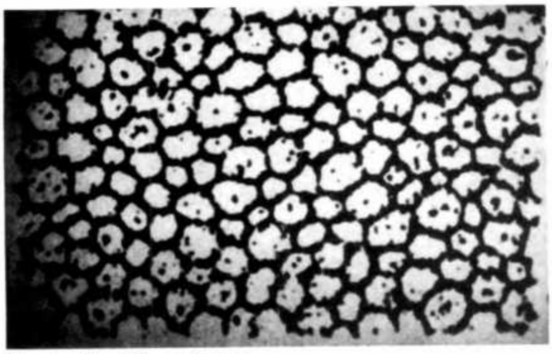

Fig. 4 *Final binary image.*

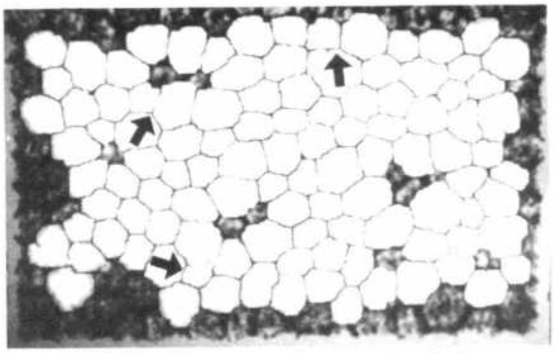

Fig. 6 *Image shown in Fig. 5 after correction. Defects are filled and fused cells are separated (arrows).*

The area of the image to be analysed is determined by arbitrarily placing a frame. The maximum and minimum thresholds are determined from the brightness histogram of the image. Binary images are prepared serially from the maximum to the minimum threshold, and the image considered to be optimal is selected (Fig. 4), so that any binary image between the maximum and the minimum threshold can be reproduced, or the entire binary conversion process can be performed again. Since the quality of the final image is greatly dependent on the determination of the optimal threshold values, these steps are extremely important for accurate judgment.

Restoration of cell boundaries. Since the shape of the cell is more or less distorted in the binary image, the original cell morphology is restored by processes such as hole filling, edge detection, removal of small particles, and removal of small particles from the outer circumference. Further, an entire cell image surrounded by a boundary can be deleted (Fig. 5).

Correction of images. Cells may be still fused or defects may be present in the cell images obtained by the above procedure. Such cells are corrected with the digitizer while overlapping the original image. Defects are filled by adding lines or planes, using a line thickness of 2 pixels, and the size of the drawing can be freely adjusted. The boundary between fused cell images is drawn similarly with a line 2 pixels in thickness (Fig. 6).

Thinning of cell boundaries. Since the boundaries between cells are still thick and irregular, the width of the boundary is reduced to 1 pixel (Fig. 7).

Labelling and measurement. This process is performed by the routine program of the image analyser.

SUBJECTS

The central area of the corneal endothelium of 30 normal eyes in 15 subjects (age 22–65 years) was photographed (f 1/2) for 20–30 seconds with the specular microscope and recorded in the VTR.

The accuracy of measurement was examined by comparing the mean endothelial cell area of each eye determined directly from the VTR images with that determined from the traced images of the same cells displayed on the video monitor and photographed with an instant camera.

The computer was programmed to calculate the time required for each of the image processing stages, and the time needed for the entire procedure and correction of images was determined.

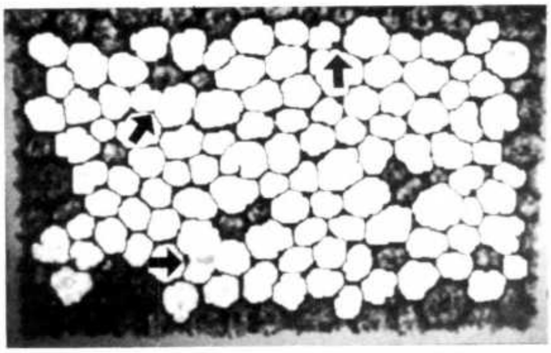

Fig. 5 *Image after overlapping of the original image. Arrows show defects and fusion of cell images.*

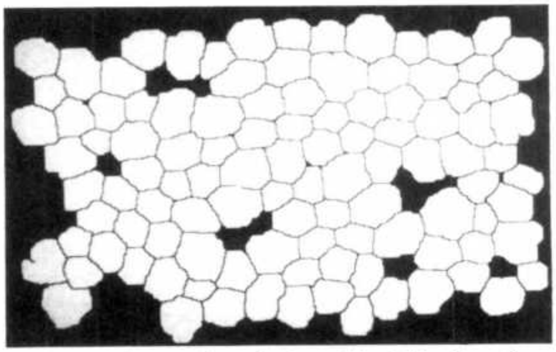

Fig. 7 *Final image after reduction of the width of the cell boundary to 1 pixel.*

Table 1 *VTR image analysis*

Patient	*Sex*	*Age*	*Mean cell area (Y) (μm²±SD)*	*No. of cells analysed*	*Time required for entire procedure (min)*	*Time required for manual correction (min)*
1	F	21	342±130	77	15·2	6·8
			353± 85	83	14·1	6·2
2	F	22	339± 88	69	13·4	4·5
			331± 96	84	11·3	3·8
3	F	23	323± 88	99	9·5	0
			336± 92	101	10·4	0
4	F	23	341± 84	88	9·3	0
			335± 91	92	9·8	0
5	F	26	359±109	86	17·9	9·0
			361±130	67	18·2	7·3
6	F	24	355±122	81	14·9	7·8
			350±129	70	16·8	4·0
7	M	36	388± 88	75	16·2	6·2
			393± 96	84	15·2	6·4
8	M	30	367±103	88	12·9	0
			355±101	114	15·2	4·8
9	M	54	391±112	98	11·5	0
			386±103	106	12·2	3·0
10	M	64	405±103	76	14·3	6·5
			417±111	71	15·7	7·9
11	F	28	362± 84	101	12·3	3·5
			350± 88	104	12·7	3·9
12	F	24	346± 88	62	12·2	0
			351± 89	54	13·9	3·3
13	F	24	332±108	97	16·5	6·3
			340±118	91	18·0	7·4
14	F	23	323± 93	98	11·3	3·5
			336±101	94	9·2	2·2
15	F	21	330± 90	101	11·5	2·3
			326± 88	98	10·0	0
Mean				87±14	13·3±2·7	3·9±2·9

Results

The regression equation between the mean cell area determined directly from the VTR images (Y) (Table 1) and that determined from the trace of the same image displayed on the monitor (×200) and photographed with an instant camera (X) (Table 2) was $Y=0{\cdot}7190X+96{\cdot}5$, $r=0{\cdot}9335$ (Fig. 8).

The mean time required for the entire procedure in all subjects was 13·3 (SD 2·7) minutes. The mean time for correction was 3·9 (SD 2·9) minutes. The number of cells analysed was 55–114 cells, mean 87 (SD 14). The number of completely automated analyses was 8 of the 30 eyes (27%).

Discussion

Our system eliminates the need for conventional photographic procedures by directly analysing VTR images, thus making cell morphometry possible immediately after taking a picture. This enables considerable economy of time and labour. Another advantage of the technique is that 10–20-second VTR film always includes at least a few very clear cell images.

Table 2 *Analysis of trace of same VTR image*

Mean cell area (X)	*No. of cells analysed*
361±126	81
363± 87	85
347± 92	83
340±101	90
314±116	104
321± 97	110
336± 84	80
325± 86	82
385±113	99
374±126	55
372±102	75
358±120	65
399±146	67
412±101	79
371±121	70
376±111	109
386± 98	86
398±118	99
415±101	80
436±128	76
353± 91	90
361± 86	85
322± 99	80
343± 92	72
326±106	88
352±128	86
335± 95	89
329± 92	92
327± 95	97
311± 97	114

Hartmann *et al.*[16] recently reported on an automated cell morphometry system using a frame memory mechanism. This method does not require the process of recording the images in VTR for subsequent analysis. Further, the signal-to-noise ratio may be higher than that of the VTR because of the digital memory system. However, as the number of frames is limited to 256, the recording time is short, and hence skilful timing is required for photographing the human eye, which is constantly moving.

On the other hand our images are recorded in the VTR. This allows a long recording time with serial exposures every 1/30 second, so that well focused and clear images of the living eyes can be readily obtained. The resolution may be reduced, which necessitates the process of selecting suitable images and inputting them into the image analyser, but these processes are simple and require only a short time.

The accuracy of an analyser in detecting cell boundaries is a matter of the greatest concern in developing automated cell morphometric techniques. Our results showed a satisfactory correlation ($r=0{\cdot}9335$) (Fig. 8) with those obtained by a tracing method using the same image data, indicating that our method can be used in the clinical setting.

The number of cells analysed by this technique was smaller (mean 87 (SD 14)) (Table 1) than that by the

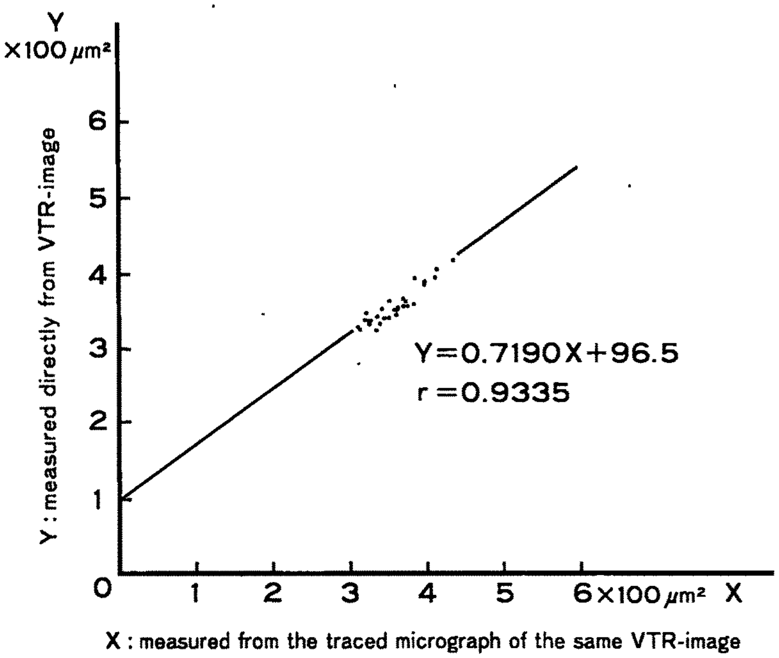

Fig. 8 *Linear regression equation between the mean cell area determined by direct automated analysis of VTR image (Y) and that determined by the trace of the same image.*

tracing method (120–150),[18–21] because the aperture was usually set at f 1/2 to obtain a deep focus and because the cells that required extensive correction were eliminated in the stage of binary conversion by setting the thresholds high. Theoretically, analysis of all cell images input into the image analyser is possible when using such a threshold. An increase in the number of cell images inputted, however, will result in an increase in the number of images with incomplete boundaries, prolongation of correction and determination time, and decrease in accuracy. Thus the number of cells analysed is primarily dependent on the quality of the original image but secondarily on the time needed for, and accuracy of, its correction. To achieve a reasonable balance among these factors—that is, to determine the threshold to be used for binary conversion and how much correction should be made to obtain adequate accuracy of the data—experienced human judgment while monitoring the image on the display is still indispensable. So we think that analysis of 50 to 120 cells, or at most 150 cells, is a sufficient number to assess corneal function in routine clinical use, for example, for quickly determining the orientation prior to intraocular lens implantations. By our technique, as well as other automated systems for cell morphometry, cell boundaries are determined by the computer, but the operator must always confirm whether it detected all boundaries correctly. Therefore completely automated systems in the true sense of the word will be realised only after the development of more sophisticated techniques.

All the currently available systems require human judgment in determining the optimal threshold and image correction in reference to the original image. However, our apparatus achieved reasonable accuracy in data processing, requiring slightly more than 10 minutes for completion of the entire procedure. The part of the procedure involving human interaction does not need excessive concentration by the operator. Therefore this technique appears to be suitable for routine clinical use.

References

1 Matsuda N, Suda T, Manabe R. Serial alterations in endothelial cell shape and pattern after intraocular surgery. *Am J Ophthalmol* 1984; **98**: 313–9.
2 Schults RO, Matsuda M, Yee RW, Edelhauser HF, Schults KJ. Corneal endothelial changes in type I and type II diabetes mellitus. *Am J Ophthalmol* 1984; **98**: 401–10.
3 Rao GH, Waldon WR, Aquavella JV. Morphology of graft endothelium and donor age. *Br J Ophthalmol* 1980; **64**: 523–7.
4 Matsuda M, Bourne WM. Long-term morphologic changes in the endothelium of transplanted corneas. *Arch Ophthalmol* 1985; **103**: 1343–6.
5 Matsuda M, Suda T, Manabe R. Quantitative analysis of endothelial mosiac pattern changes in anterior keratoconus. *Am J Ophthalmol* 1984; **98**: 43–9.
6 Karai I, Matsumura S, Takise S, Horiguchi S, Matsuda M. Morphological change in the corneal endothelium due to ultraviolet radiation in welders. *Br J Ophthalmol* 1984; **68**: 544–8.
7 Glasser DB, Matsuda M, Ellis JG, Edelhauser HF. Effects of

irrigating solutions on the corneal endothelium after in vivo anterior chamber irrigation. *Am J Ophthalmol* 1985; **99:** 321–8.

8 Laing RA, Sandstrom MM, Berrospi AR, Leibowitz HM. Changes in the corneal endothelium as a function of age. *Exp Eye Res* 1976; **22:** 587–94.

9 Waring GO, Krohn MA, Ford GE, Harris RR, Rosenblatt HL. Four methods of measuring human corneal endothelial cells from specular photomicrographs. *Arch Ophthalmol* 1980; **98:** 848–55.

10 Nishi O, Hanasaki K. Corneal endothelial damage following cataract surgery and intraocular lens implantation. *Jpn J Clin Ophthalmol* 1983; **37:** 13–7.

11 Sato T. Studies on the endothelium of the corneal graft. *Jpn J Ophthalmol* 1978; **22:** 114–26.

12 Shaw EL, Rao GN, Arthur EJ, Aquavella JV. The functional reverse of corneal endothelium. *Ophthalmology* 1978; **85:** 640–9.

13 Lester JM, McFarland JL, Bursell SE, Laing RA, Brenner JF. Automated morphometric analysis of corneal endothelial cells. *Invest Ophthalmol Vis Sci* 1981; **20:** 407–10.

14 Hartmann C, Weingart M, Dünner P, Giraud JP. Automatisierte endothelmorphometrie. 1982; **79:** 261–5.

15 Hirst LW, Sterner RE, Grant DG. Automated analysis of wide-field specular photomicrographs. *Cornea* 1984; **3:** 83–7.

16 Hartmann C, Köditz W. Automated morphometric endothelial analysis combined with video specular microscopy. *Cornea* 1985; **3:** 155–67.

17 Nishi O. Direct measurement of the corneal endothelial cell area on the negative film. *Nippon Ganka Gakkai Zasshi* 1985; **89:** 1120–4.

18 Sawa M, Tanishima T. The morphometry of the human corneal endothelium and follow-up of postoperative changes. *Jpn J Ophthalmol* 1979; **23:** 337–50.

19 Inoda S, Ohkubo A, Tatsui T, Ohara K. Topographical Morphometry of the human corneal endothelium using new parameters. *Folia Ophthalmol Jpn* 1983; **34:** 1002–9.

20 Kandori T, Sawa M, Tanishima T. Computerized morphometry of the human corneal endothelium. *Nippon Ganka Gakkai Zasshi* 1981; **85:** 1204–7.

21 Komine T, Oikawa T. Analysis of specular photomicrography with a computerized digitizer and an image analyzer. *Nippon Ganka Gakkai Zasshi* 1981; **85:** 457–63.

Accepted for publication 13 November 1986.

British Journal of Ophthalmology, 1988, **72**, 74–77

Acute posterior multifocal placoid pigment epitheliopathy and sarcoidosis

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SUMMARY We report on a patient with acute posterior multifocal placoid pigment epitheliopathy and sarcoidosis. A review of the literature suggests that sarcoidosis may occur more commonly in this condition than previously suspected.

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) was originally defined by Gass[1] and is characterised by the acute onset of multiple lesions of the posterior pole at the level of the retinal pigment epithelium. It has become clear that this condition may be only one feature of more generalised disease, and various reports have linked APMPPE with transient cerebral disturbances, cerebral vasculitis,[2-4] erythema nodosum,[5 6] subclinical nephropathy,[7] and thyroiditis.[8] A review of the ocular fundus findings in a series of patients with sarcoidosis[9] found retinal pigment epithelial changes in 36% of 36 cases. In this group, the lesions were usually not at the posterior pole, and in no patient was vision affected by the retinal pigment disturbance. APMPPE has not been previously thought to be associated with sarcoidosis.

Case report

In March 1981 a 24-year-old male trainee designer became unwell with an influenza-like illness followed 10 days later by the development of multiple scotomata in his visual field. Examination of the fundi revealed multifocal placoid grey/white lesions at the posterior pole of both eyes (Fig. 1). A subsequent fluorescein angiogram displayed the typical features of APMPPE, namely, hypofluorescence in the early dye transit and marked hyperfluorescence in the late dye transit phase. The features were those of APMPPE. The visual symptoms improved without specific therapy, and the lesions regressed. Six weeks later he presented with bilateral anterior uveitis. Topical steroid treatment was begun, but he remained systemically unwell and developed recurrent small buccal ulcers. Two weeks prior to his admission to the Neurological Centre he was noted to have a generalised lymphadenopathy and complained of an ascending sensory disturbance involving the left leg. For 24 hours before admission he had hesitancy of micturition.

Examination revealed cervical, inguinal, and axillary lymphadenopathy. The blood pressure was 120/80 mmHg. The visual acuity was 6/6 bilaterally, and paracentral scotomata were present in both visual fields. The fundal appearances were unchanged. Neurological examination showed him to have increased tone in both lower limbs, pathologically brisk reflexes, and flexor plantar responses. There were also radicular signs, with fifth lumbar motor weakness and disturbed sensation in the first to fourth sacral dermatomes on the left side. Clinically he was thought to have a myeloradiculopathy.

He had a haemoglobin of 10·7 g/dl, with normal normochronic normocytic indices, a raised erythrocyte sedimentation rate of 61 mm/h (Westergren), and raised serum urea and creatinine concentrations of 11·3 mmol/l and 207 µmol/l respectively. Serum proteins with electrophoresis and urine microscopy were normal. A chest radiograph revealed bilateral hilar enlargement, but plain radiology of the abdomen and intravenous nephrograms were normal. A myelogram and subsequent examination of the cerebrospinal fluid showed no abnormality. A lymph node biopsy was performed, and histological examination showed multiple epithelioid granulomata

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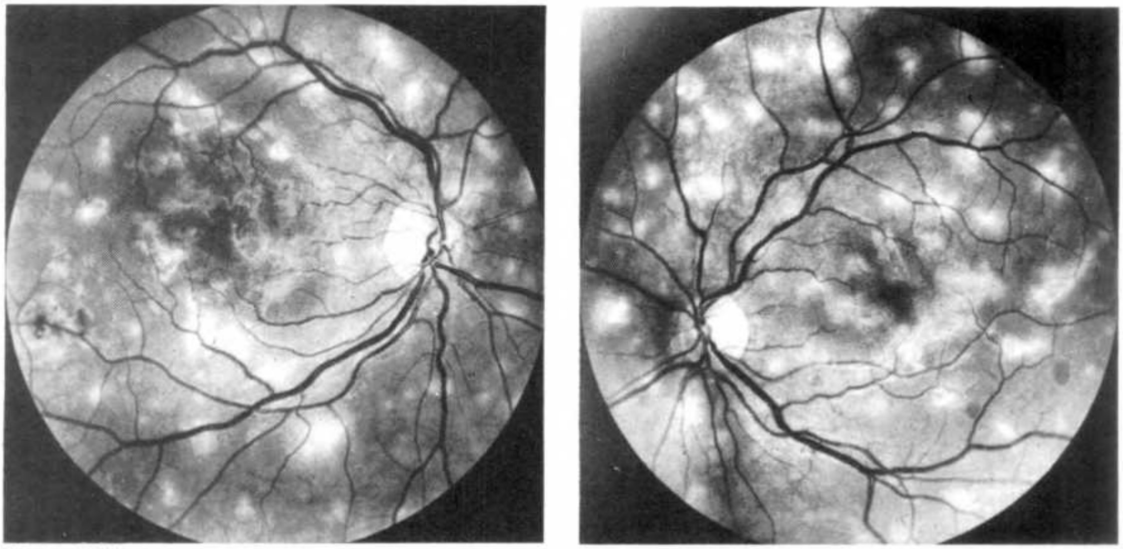

Fig. 1 *Right eye.* Fig. 2 *Left eye.*

Fig. 1 *Fundal appearances of both eyes showing multifocal grey/white lesions at the posterior poles.*

containing numerous Langhans giant cells and occasional central necrosis. No acid fast bacilli were seen and a Mantoux test was negative. Serum angiotensin converting enzyme activity was 52 nmol ml^{-1} min^{-1} (normal 16-52).

A renal biopsy showed a cortico-medullary sample with II glomeruli (Fig. 2). There were focal capsular adhesions, slight wrinkling of some basement membranes, considerable numbers of non-caseating granulomata with multinucleate giant cells, and occasional crystalline inclusions. The majority of these granulomata were present interstitially and occasionally surrounded tubules. There was a moderate diffuse interstitial infiltrate of lymphocytes and plasma cells. Early tubular atrophy involved some 20% of the tubules. The appearances were

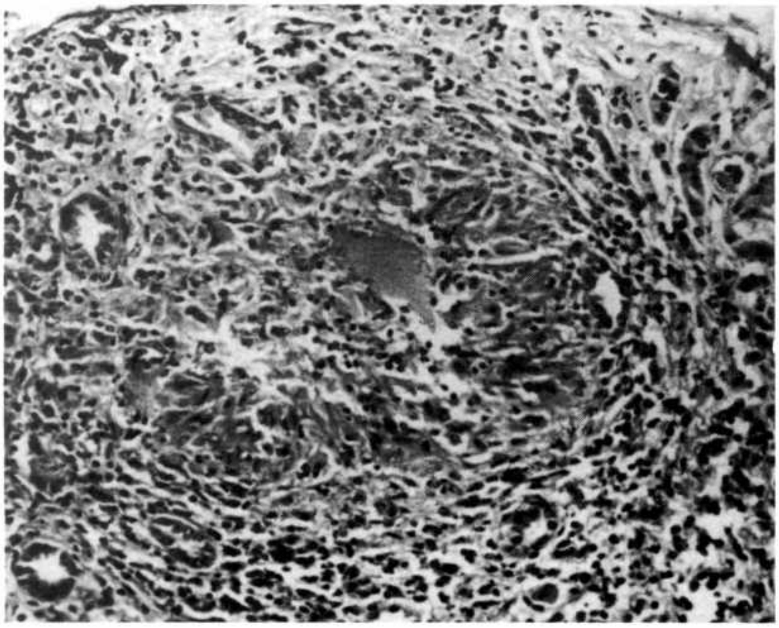

Fig. 2 *Renal biopsy containing non-caseating granuloma. See text for details. Haematoxylin and eosin.* ×*236.*

those of an interstitial granulomatous nephritis with features suggestive of sarcoidosis. Immunofluorescence examination showed no significant immunoglobulin deposition. Electron microscopy showed a small number of electron dense deposits on the glomerular basement membrane with focal thickening and wrinkling. Examination of sarcoid granulomata showed lymphocytes and macrophages and considerable fibroblastic activity.

A diagnosis of sarcoidosis was made and treatment started with prednisolone 60 mg daily, which was followed by a gradual resolution of his symptoms. Three months later, when he was taking 20 mg of prednisolone daily, no active ocular disease was evident, and apart from a small area of disturbed sensation over the left buttock he was neurologically normal. The serum urea concentration was 9·2 mmol/l and the creatinine 126 μmol. Eighteen months after starting steroid therapy he was asymptomatic, and the serum urea and concentration were normal.

Discussion

Sarcoidosis affects the eye and optic nerve in many ways, and some 20% of patients will have ocular involvement at the time of their first examination. In established disease the incidence is even higher.[10] Anterior segment disease occurs most commonly and usually takes the form of a chronic granulomatous uveitis. Posterior segment involvement occurs less frequently and rarely in isolation – chorioretinitis, periphlebitis, and chorioretinal nodules are the lesions most frequently described.[10,11] Retinal pigment epithelial changes usually occur peripherally and are not associated with a disturbance of vision.[9] Vitreous opacities[12] and choroidal granulomas[13] also occur. Disease outside the globe is equally varied – conjunctivital and lacrimal gland involvement, papilloedema, and direct granulomatous involvement of the optic nerve or chiasm[14] are all well described.

APMPPE usually occurs in young adults, who develop an acute bilateral disturbance of vision. Funduscopy reveals multiple, grey-white, flat placoid retinal lesions at the level of the retinal pigment epithelium, and there may also be an associated low grade uveitis. Characteristically, fluorescein angiography shows hypofluorescence in the early dye transit and hyperfluorescence in the late transit phase. Gass[1] thought the disease originated in the retinal pigment epithelium, although later authors suggested that the lesions may be due to an underlying choroidal vasculitis[5,15] The pathophysiological mechanism is now thought to be choroidal ischaemia, which leads to a disturbance of the retinal pigment – epithelium barrier.[16,17]

Several disorders have been reported to occur with APMPPE. Symptoms suggestive of an antecedent viral attack are common,[18] but firm serological evidence of definite infection has only been occasionally documented.[19] The central nervous system (CNS) has been unequivocally involved in several cases, and the symptoms included headache, drowsiness, and focal neurological deficit due to lesions of the cerebral hemisphere.[2,4] Investigations in these cases have shown minimal, non-specific abnormalities of the electroencephalogram, a lymphocytic pleocytosis in the cerebrospinal fluid,[20] and cerebral infarction shown by a computerised tomography scan of the head.[4] Carotid and vertebral angiography in three cases purported to show changes of cerebral vasculitis[2-4] and led to the suggestion that APMPPE may be part of a systemic vasculitis. Some support for this suggestion comes from its association with erythema nodosum[5,6] and the presence of cellular casts in the urine of patients with APMPPE.[7] Erythema nodosum may be due to a cutaneous vasculitis, and urinary casts might indicate a subclinical microvascular nephropathy.

There can be no doubt that our patient suffered from renal and central nervous system sarcoidosis, and to our knowledge this is the first report which links this disorder with APMPPE. It is important to review the neurological case reports in the light of this association. In fact many of the non-specific symptoms described such as headache and drowsiness may occur in CNS sarcoid, and cerebral infarction with focal neurological deficit may be the result of granuloma formation with blood vessel walls.[21] Abnormalities of the electroencephalogram and a lymphocytic pleocytosis in the cerebrospinal fluid also occur in sarcoidosis. Furthermore, erythema nodosum is a common cutaneous manifestation of the disease. None of the patients described in these reports had specific tests for sarcoidosis. We suggest that some of these cases may have had sarcoidosis and that this disorder should be considered when investigating patients with APMPPE in future.

References

1 Gass JDM. Acute posterior multifocal placoid pigment epitheliopathy. *Arch Ophthalmol* 1968; **80**: 177–85.

2 Holt WS, Regan CDJ, Trempe C. Acute posterior multifocal placoid pigment epitheliopathy. *Am J Ophthalmol* 1976; **81**: 403–12.

3 Sigelman J, Behrens M, Hilal S. Acute posterior multifocal placoid pigment epitheliopathy associated with cerebral vasculitis and homonymous hemianopia. *Am J Ophthalmol* 1979; **88**: 919–24.

4 Smith CH, Savino PJ, Beck RW, Schatz NJ, Sergott RC. Acute posterior multifocal placoid pigment epitheliopathy and cerebral vasculitis. *Arch Neurol* 1983; **40**: 48–50.

5 Deutman AF, Oosterhuis JA, Boen-Tan TN, Aan De Kerk AL. Acute posterior multifocal placoid pigment epitheliopathy. *Br J Ophthalmol* 1972; **56**: 863–74.

6 Van Buskirk EM, Lessell S, Friedman E. Pigmentary epitheliopathy and erythema nodosum. *Arch Ophthalmol* 1971; **85:** 369–72.
7 Priluck IA, Robertson DM, Buettner H. Acute posterior multifocal placoid pigment epitheliopathy. *Arch Ophthalmol* 1981; **99:** 1560–4.
8 Jacklin HN. Acute posterior multifocal placoid pigment epitheliopathy and thyroiditis. *Arch Ophthalmol* 1977; **95:** 995–7.
9 Spalton DJ, Sanders MD. Fundus changes in histologically confirmed sarcoidosis. *Br J Ophthalmol* 1981; **65:** 348–58.
10 Obenauf CD, Shaw HE, Sydnor CF, Klintworth GK. Sarcoidosis and its ophthalmic manifestations. *Am J Ophthalmol* 1978; **86:** 648–55.
11 Gould H, Kaufman HE. Sarcoid of the fundus. *Arch Ophthalmol* 1961; **65:** 453–6.
12 Landers PH. Vitreous lesions observed in Boeck's sarcoid. *Am J Ophthalmol* 1949; **32:** 1740–1.
13 Campo RV, Aaberg TM. Choroidal granuloma in sarcoidosis. *Am J Ophthalmol* 1984; **97:** 419–27.
14 Blain JG, Riley W, Logothetis J. Optic nerve manifestations of sarcoidosis. *Arch Neurol* 1965; **13:** 307–9.
15 Kirkham TH, ffytche TJ, Sanders MD. Placoid pigment epitheliopathy with retinal vasculitis and papillitis. *Br J Ophthalmol* 1972; **56:** 875–80.
16 Savino PJ, Weinberg RJ, Yassin JG, Pilkerton RA. Diverse manifestations of acute posterior multifocal placoid pigment epitheliopathy. *Am J Ophthalmol* 1974; **77:** 659–62.
17 Bird AC, Hamilton AM. Placoid pigment epitheliopathy. *Br J Ophthalmol* 1972; **56:** 881–6.
18 Ryan SJ, Maumenee EA. Acute posterior multifocal placoid pigment epitheliopathy. *Am J Ophthalmol* 1972; **74:** 1066–74.
19 Azar P, Gohd RS, Waltman D, Gitter KA. Acute posterior multifocal placoid pigment epitheliopathy associated with an adenovirus type 5 infection. *Am J Ophthalmol* 1975; **80:** 1003–5.
20 Bullock JD, Fletcher RL. Cerebrospinal fluid abnormalities in acute posterior multifocal placoid pigment epitheliopathy. *Am J Ophthalmol* 1977; **84:** 45–9.
21 Matthews WB. Neurosarcoidosis. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology*. Vol Amsterdam: North Holland, 1979; **38:** 521–42.

Accepted for publication 11 August 1986.

British Journal of Ophthalmology, 1988, **72**, 78

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Cranial nerve palsy following retrobulbar anaesthesia

SIR, Retrobulbar injection of anaesthetic agents is seldom associated with serious sequelae. Complications such as retrobulbar haemorrhage, central retinal artery occlusion, scleral perforation, grand mal seizures, and cardiopulmonary arrest have, however, been described. We wish to report an additional complication of retrobulbar anaesthesia: temporary contralateral second and third cranial nerve dysfunction accompanied by a depressed sensorium.

Case report

A 66-year-old white male without significant past medical history complained of sudden loss of his inferior visual field in his left eye. Best-corrected visual acuity was 20/30 in the right eye and 20/40 in the left eye. Pupils were equal round and reactive to light and versions were full. Slit-lamp biomicroscopy of the anterior segments revealed early nuclear sclerosis. Tensions by applanation tonometry were 14 mm Hg in both eyes. Funduscopic examination was remarkable for lattice degeneration in both eyes and a superior retinal detachment in the left eye. While dilated, retrobulbar anaesthesia was administered to the left eye using 3 ml of 2% lignocaine without epinephrine and a disposable ultrasharp tip needle. Air was then injected into the left eye to tamponade the retinal break located at the 12 o'clock meridian. After the procedure was completed the patient complained of decreased vision in his other eye and became disorientated. Visual acuity in the right eye was hand motion. The patient was unable to elevate, depress, or adduct the eye.

Right cranial nerves four and six were intact. Blood pressure, pulse, and respiratory rate were stable, and there were no other neurological findings except for an altered mental status. He was both incoherent and disorientated to time and place. Approximately one hour after the onset of symptoms the patient's visual acuity improved to 20/40 in the right eye, and versions were again full. He became coherent and orientated to time and place.

Discussion

Injection of local anaesthetics into the optic nerve sheaths and subsequently into the intracranial cavity has been proposed as the mechanism of central nervous system complication following retrobulbar anaesthesia. In five patients who underwent retrobulbar injection, orbitography demonstrated radio-opaque dye penetrating the optic nerve sheaths and tracking into the subdural space.[1] The contrast material outlined the optic nerve and extended through the optic canal into the middle cranial fossa. In all cases the injection was believed to be uncomplicated. This pathway has similarly been demonstrated in cadavers.[2]

Animal studies have shown that direct injection of anaesthetic into the optic nerve results in nerve fibre degeneration.[3] Paulter *et al.* reported two cases of marked visual loss resulting from retrobulbar injections presumably into the optic nerve sheath.[4] Callahan suggests that the likelihood of penetrating the optic nerve is increased when disposable needles are used.[5] These needles are ultrasharp, and consequently it is difficult to appreciate the resistance of the optic nerve sheath.

The patient presented illustrates contralateral second and third cranial nerve dysfunction as a complication of retrobulbar anaesthesia induced with an ultrasharp needle. We believe a significant concentration of anaesthetic reached the optic nerve chiasm and/or contralateral optic nerve to block nerve conduction. The contralateral nerve palsy resolved once the anaesthetic was metabolised. The patient's disorientation suggests that the anaesthetic agent also entered the subarachnoid space and the cerebrospinal fluid. Recently, Antoszyk and Buckley reported three cases of contralateral second and third nerve palsy,[6] and Friedberg and Kline described two cases of contralateral second nerve palsy[7] following retrobulbar anaesthesia using ultrasharp needles. Many authors recommend the use of blunt tip needles and having the patient look straight ahead or down and outward during retrobulbar injection to minimise the chance of penetrating the optic nerve sheath.[5,6] We feel this will reduce the incidence of complications following retrobulbar injection.

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References

1 Reed JW, MacMillan AS, Lazenby GW. Transient neurologic complications of positive contrast orbitography. *Arch Ophthalmol* 1969; **81**: 508–11.
2 Drysdale DB. Experimental subdural retrobulbar injection of anaesthesia. *Ann Ophthalmol* 1984; **16**: 716–8.
3 Linn JG Jr. The effects of injection of anesthetic solutions into the optic nerve. *Am J Ophthalmol* 1957; **43**: 471.
4 Paulter SE, Grizzard WS, Thompson LN, Wing GL. Blindness following retrobulbar injection into the optic nerve. *Ophthalmic Surg* 1986; **17**: 334–7.
5 Callahan A. Ultrasharp disposable needles. *Am J Ophthalmol* 1966; **62**: 173.
6 Antoszyk AN, Buckley EG, Contralateral decreased visual acuity and extraocular muscle palsies following retrobulbar anesthesia. *Ophthalmology* 1986; **93**: 462–5.
7 Friedberg HL, Kline OR Jr. Contralateral amaurosis after retrobulbar injection. *Am J Ophthalmol* 1986; **101**: 688–90.

Branch retinal arteriolar occlusion with chicken-pox

SIR, A 19-year-old male who had developed the typical rash of chicken-pox three days previously was referred by his general practitioner after noticing a 'haze' in the nasal field of his left eye that day. On examination his visual acuity was 6/4 in each eye unaided. Examination of his visual fields to confrontation revealed a left inferonasal quadrantic defect. The eyes were quiet and the pupillary responses were normal. Fundal examination revealed a left superotemporal branch arteriole occlusion, with a corresponding area of

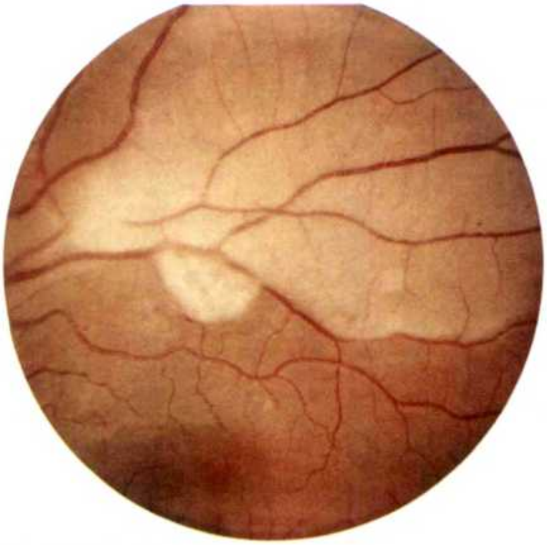

Fig. 1 *Left fundus on admission.*

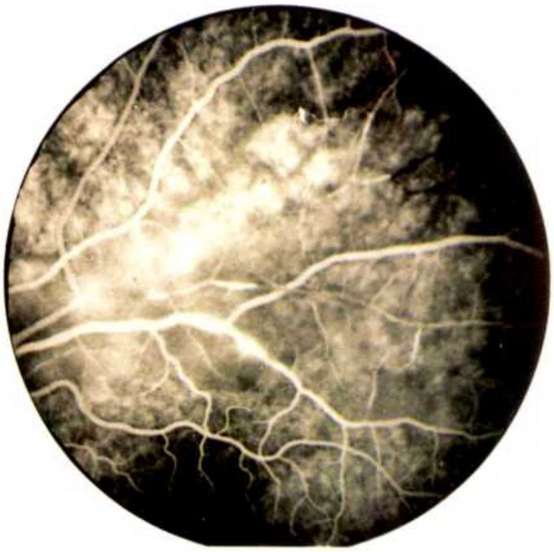

Fig. 2B *Late fluorescein angiogram of left fundus.*

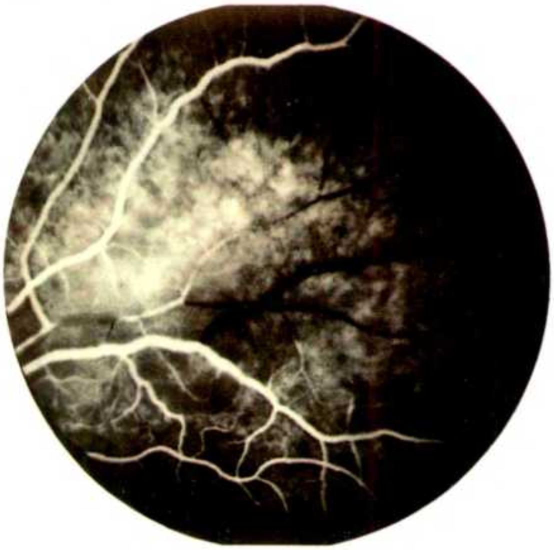

Fig. 2A *Early fluorescein angiogram of left fundus.*

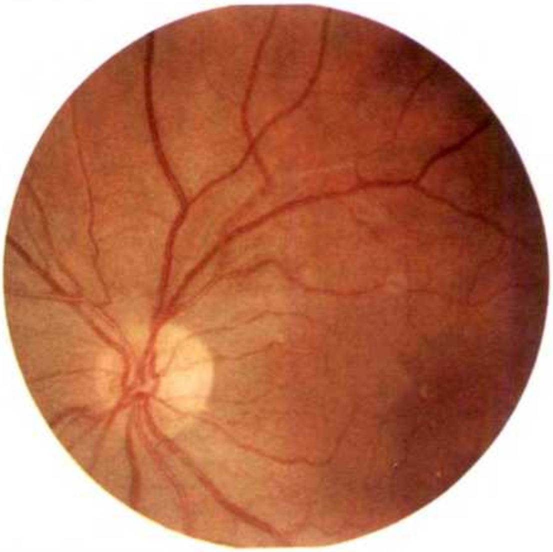

Fig. 3 *Left fundus five months later.*

oedema (Fig. 1). Immediate treatment with intravenous acetazolamide and eye massage proved unsuccessful. General examination was unremarkable, apart from a just palpable liver which resolved within five days. The following investigations gave normal results: full blood count and platelets, erythrocyte sedimentation rate, plasma viscosity, protein electrophoresis, fasting glucose and lipids, serology for syphilis, and urine analysis. Liver function tests revealed raised aspartate transaminase and γ-glutamyl transferase levels, but these fell markedly in five days and were entirely normal after a further week. Fluorescein angiography (Figs. 2 A, B) confirmed the arteriolar obstruction with delayed filling of the corresponding vein. Late films demonstrated a slight leakage of dye around that vein, but we did not consider this signified a focal vasculitis.

The retinal oedema settled over the subsequent four months, though the appearance of the arteriole remained the same (Fig. 3), and a visual field test after five months showed that the defect remained unchanged (Fig. 4). Throughout this period his central visual acuity was unaffected.

Discussion

Serious complications following chicken-pox are fortunately rare[1] and the published reports of visual disturbances

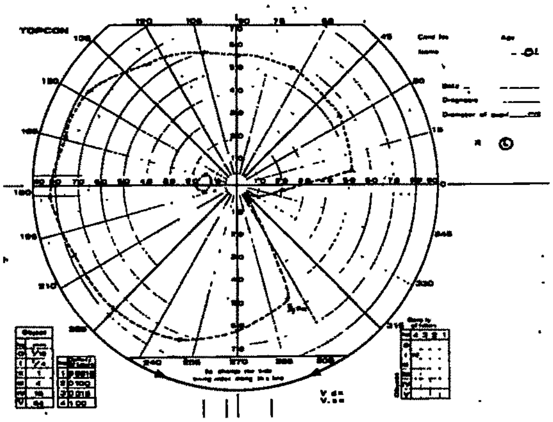

Fig. 4 *Left visual field five months later.*

occuring with it are few.[2] One case was associated with unilateral[3] and two with bilateral[4,5] optic nerve involvement, and one other was in a patient with bilateral papillitis and a unilateral macular lesion,[6] but all reported a good visual recovery. The only report of a permanent visual field defect[7] was in a 16-year-old girl, occurring on the fourth posteruptive day. This is similar to our patient, who developed a field defect three days after the onset of his rash. In that report the field defect was associated with segmental optic disc pallor followed by pigmentation, and the authors suggested that this was caused by a focal optic neuritis. This may have had an ischaemic basis and therefore could represent a similar process to the arteriolar obstruction in our patient. Although there are no reports of retinal arteriolar occlusion associated with varicella zoster, many complications of the closely related herpes zoster virus may have an ischaemic basis,[8] either a retinal vasculitis or perivasculitis[9] or a granulomatous angiitis affecting the brain.[10] In addition the acute retinal necrosis syndrome, which includes an arteritic component, has been linked with a member of the herpes virus group.[11] However there was no evidence of a more widespread vasculitis in our patient, and no source for an embolus was found. The exact cause of the retinal arteriolar occlusion in this case remains unknown, but its coincidence with chicken-pox is interesting. To the best of our knowledge this is only the second reported case where a permanent visual field defect has occurred.

Our grateful thanks are due to Mr D L Hunter for kindly allowing us to report this case and for reviewing the manuscript, and to Miss Yvonne Bartlett of the Department of Medical Photography, Queen Mary's Hospital, Sidcup, Kent.

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References

1 Macleod J, ed. *Davidson's principles and practice of medicine.* Edinburgh: Churchill Livingstone, 1984: 730.
2 Duke-Elder S. *System of ophthalmology.* London: Kimpton. 1976; **15:** 167.
3 Ford FR. *Diseases of the nervous system in infancy, childhood and adolescence.* Springfield, Illinois: Thomas, 1966: 576–77.
4 Hatch HA. Bilateral optic neuritis following chickenpox. *J Pediatr* 1949; **34:** 758–9.
5 Liioi JA, Aiello MV. Bilateral papilloedema with chickenpox. *J Pediatr Ophthalmol Strabismus* 1970; **7:** 155.
6 Copenhaver M. Chickenpox with retinopathy. *Arch Ophthalmol* 1966; **75:** 199.
7 Taylor DSI, ffytche TJ. Optic disc pigmentation associated with a field defect following chickenpox. *J Pediatr Ophthalmol Strabismus* 1976; **13:** 80–3.
8 Liesegang TJ. The varicella zoster virus: systemic and ocular features. *J Am Acad Dermatol* 1984; **11:** 165–91.
9 Naumann G, Gass JDM, Font RL. Histopathology of herpes zoster ophthalmicus. *Am J Ophthalmol* 1968; **65:** 533–41.
10 Blue MC, Rosenblum WI. Granulomatous angiitis of the brain with herpes zoster and varicella encephalitis. *Arch Pathol Lab Med* 1983; **107:** 126–8.
11 Culbertson WW, Blumenkranz MS, Haines H, Gass JDM, Mitchell KB, Norton EWD. The acute retinal necrosis syndrome Part 2: Histopathology and etiology. *Ophthalmology* 1982; **89:** 1317–25.

Notes

Names omitted

Sir, We apologise for having omitted in error the names of two coworkers, Gisèle Soubrane, MD, and Peirre Dhermy, MD, in the paper entitled 'Adenocarcinoma of retinal pigment epithelium' *Br J Ophthalmol* 1987; **71:** 516–20. The correct list of authors should have been: C Ramahefasolo, G. Soubrane, P Dhermy, V Godel, L Regenbogen, G Coscas.

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Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

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ASTM CODEN BJOPAL 72 (1) 1–80 (1988) ISSN 0007-1161

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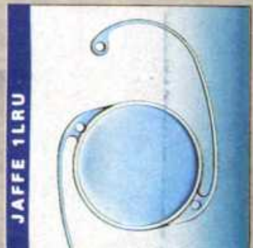

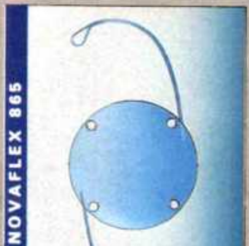

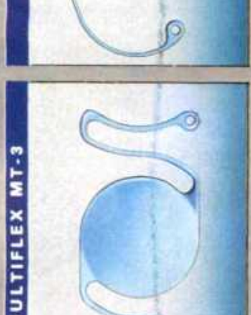

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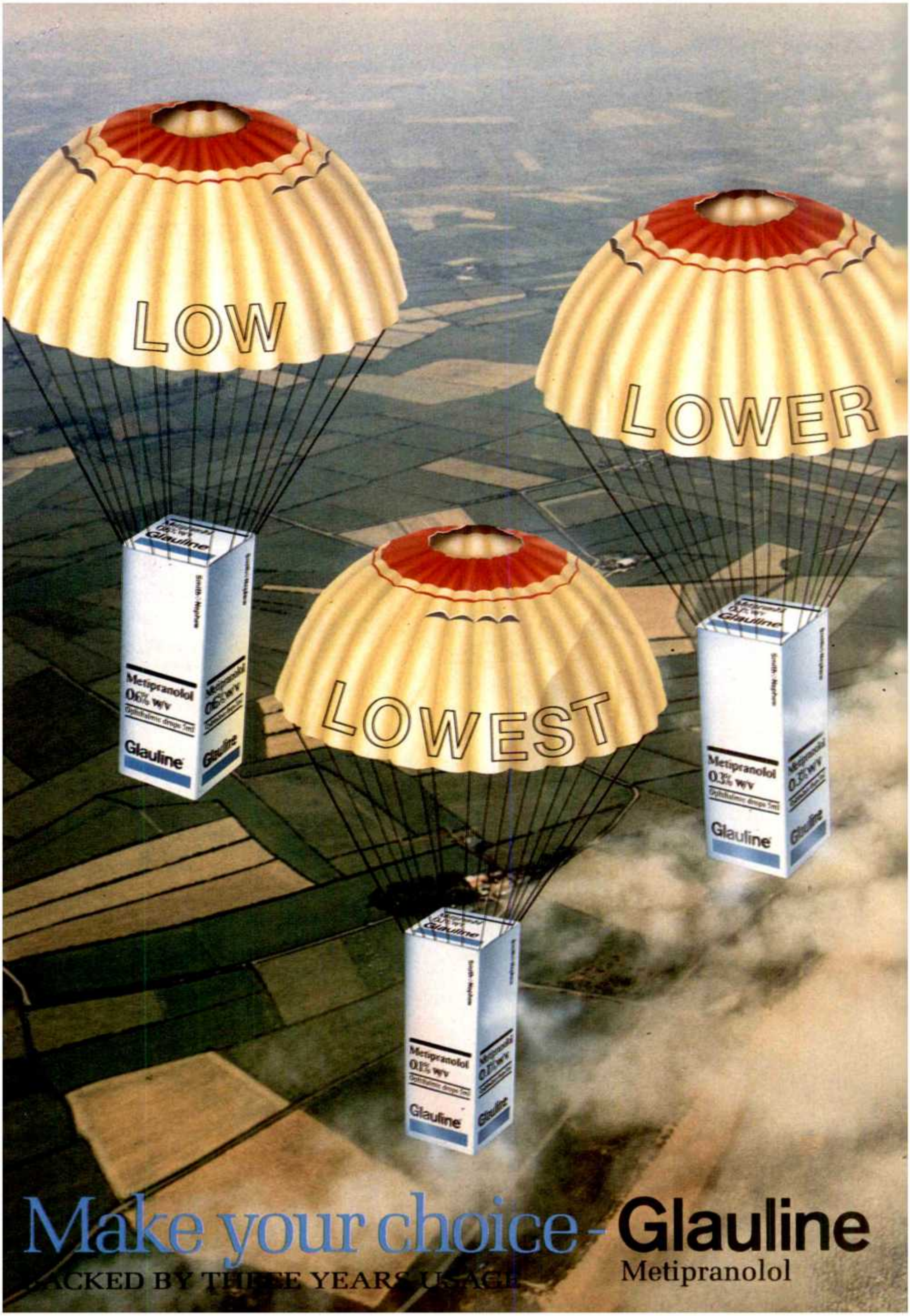
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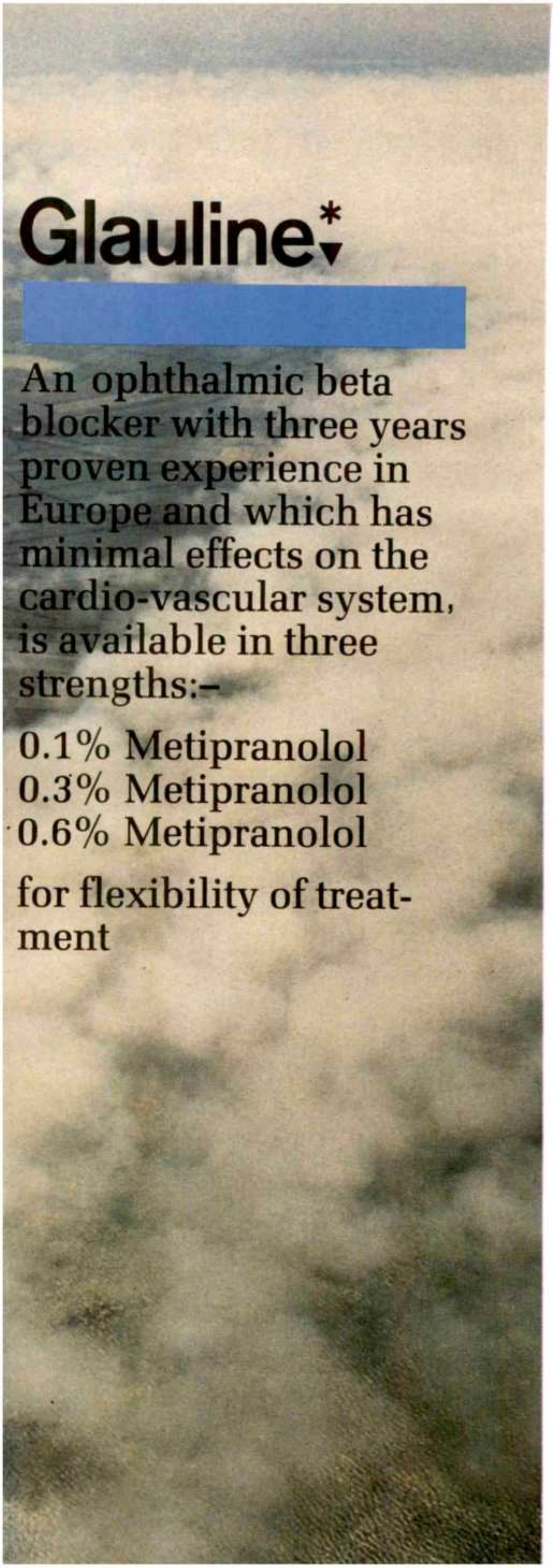
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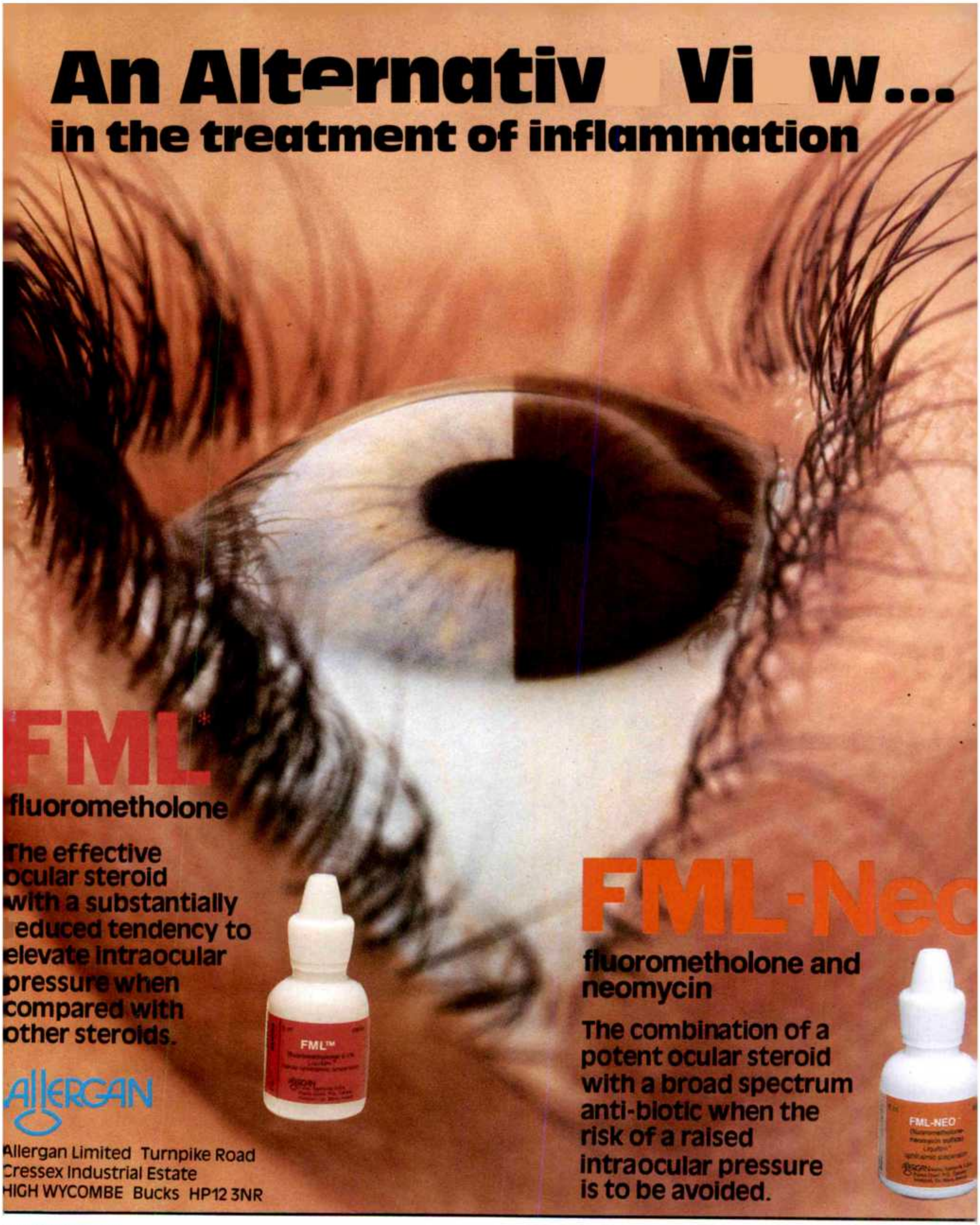

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British Journal of Ophthalmology, 1988, **72**, 81–82

Editorial: Progress in uveitis

Until recently uveitis has been a graveyard in ophthalmology. A period of enthusiasm for the subject before the second world war led only to the conclusion that tuberculosis, syphilis, or 'septic foci' did not account for the vast majority of clinical disease. The subject then lay dormant until the 1960s, when toxoplasmosis and toxocara were identified as clinical entities, but in recent years the advances in general immunology, together with the discovery of an animal model for posterior uveitis, have produced a rapidly expanding interest in the field, and it is likely that the elucidation of uveitic disease will be one of the greatest areas of advancement in ophthalmology over the next 10 years.

Initial hope in the understanding of acute anterior uveitis (AAU) came with the discovery of the high prevalence of the HLA B27 tissue type in reactive arthropathies and AAU, indicating a strong genetic susceptibility to the disease. Further progress with AAU has been disappointing, and the inconsistencies in the interpretation of the genetic data have become more apparent and baffling. About 8% of the Caucasian population carry the B27 tissue type, but only a minority will ever develop AAU or a reactive arthropathy. 97% of patients with ankylosing spondylitis are B27-positive, yet only 20% can ever expect to suffer an attack of AAU. In patients presenting with AAU about 50% are positive for B27, yet these patients have identical (though often more severe disease) to those that are negative. Obviously other genetic or environmental factors must be important, but searches for these have so far been unrewarding. α_1 Antitrypsin is a major proteolytic enzyme system and it was suggested that a deficiency of or change in the phenotype of this enzyme might be an important additional factor in predicting susceptibility or severity, as these patients could conceivably have difficulty in removing harmful proteases. Further studies in our department, however, suggest that, though there is a low level of association with the PMz antitrypsin phenotype, this does not seem very clinically significant. Another area of recent interest has been whether or not the bowel flora has a role in the initiation or relapse of AAU. Levels of IgA also tend to be raised, which would support this concept. Initial work concerned klebsiella, but this has widened in scope, and rheumatologists have found that in ankylosing spondylitis there is a cross reactivity between the lymphocytes from B27+ individuals and the enteric bacteria or a supernatant from their culture, which lyses their lymphocytes.[1] Although localisation of the disease to the spine or eye remains to be explained, this seems to be the most interesting and exciting prospect in this field, and, as before, further developments in the understanding of AAU are likely to ride on the backs of the rheumatologist.

Progress in understanding posterior uveitis (a completely different disease from AAU) has increased owing to the discovery of retinal S antigen and an animal model which can produce a posterior or panuveitis depending on the species used (probably reflecting whether or not the retina has a separate vascular supply), the dose given, and the method and route of administration. Genetic factors are important, as some species of rat are more susceptible than others. It is still not known whether or not retinal S antigen is an important factor in human disease. It was initially thought of as a possible explanation for sympathetic uveitis, but there are in fact some wide disparities. For instance, most cases of sympathetic uveitis involve trauma to the anterior segment where S antigen is not found; attempts have been made to explain this by suggesting that the various cells involved have a common origin from neuroectoderm.[2] Animal disease varies according to the dosage of antigen given, whereas the clinical severity of sympathetic uveitis does not correlate with the extent of the original injury. Sensitisation to S antigen can be found in a variety of human conditions, such as pars planitis, sarcoid, toxoplasmosis, and birdshot choroiditis, and there does not seem to be any one condition where it can be identified as the single aetiological factor. It remains to be seen whether in a disease such as toxoplasmosis it is released by retinal destruction to be an important factor in producing inflammation or is merely an epiphenomenon. Evidence against its importance is that sensitivity to the antigen does not seem to correlate with disease activity. Polyclonal antibodies to S antigen can be found in healthy people without ocular disease, and it has been suggested that complexes containing anti-S antibodies may indeed have a protective immunomodulatory role in retinal vasculitis by idiotype mechanisms.[3] Some of these contrasts may be explained when careful longitudinal studies of well defined types of uveitis are published.[4] There now appears to be a family of uveogenic retinal proteins such as rhodopsin and interreceptor binding protein; many of these molecules may have several antigenic sites, and so there is every possibility for complex interactions and modulation.

Another aspect with idiopathic posterior uveitis has been to look for evidence of systemic abnormalities which might point to the pathogenesis or aid in the diagnosis or monitoring of disease activity and treatment. Not surprisingly immunological abnormalities can be found in patients whose uveitis is associated with systemic disease (sarcoid, Behçet's syndrome, etc.) but these reflect the systemic disease as a whole rather than the ocular events, which are likely to only make a very small contribution to the complete picture.

Previous work on idiopathic posterior uveitis looking for abnormalities in immunoglobulins, immune complexes, or ocular and non-specific autoantibodies has largely been unexciting, and attention has recently been focused on changes in the T and B cell lymphocyte populations obtained from peripheral blood or the eye during surgery. Much of the work has been confused by difficulties in defining diagnostic categories, disease activity, or the effects of treatment and the failure to look at patients in relapse and remission. In the normal person approximately two-thirds of all lymphocytes are T cells, two-thirds of this group are T helper cells (T_H) and the remainder T cytotoxic and suppressor cells (T_S). Studies on AAU have shown no clear changes in T_H and T_S subsets in relapse or remission though many claims have been made. In posterior uveitis, where the inflammation is often more prolonged and severe, changes in T cell subsets have been found. A study from the National Institutes of Health (NIH)[5] found no difference in the percentages of T_H and T_S cells in a group of patients with posterior uveitis, but when the results were compared as a T_H/T_S ratio patients with active disease were found to have abnormal ratios due to an increase in T_S numbers. Studies of lymphocytes obtained from the eye during surgery are more interesting. They have usually shown that T cells predominate, and the question has been how far these and their subsets reflect active involvement as it would be likely that some cells are present merely as passengers. An interesting paper in this issue of the *BJO* using a sophisticated technique shows that a substantial proportion (20–50%) of the intraocular T cells were activated. Aqueous cell subsets reflected the peripheral blood picture whereas vitreous infiltrates did not. Interestingly, patients with idiopathic uveitis also had increased levels of activated T_H cells in the peripheral blood, suggesting that the ocular inflammation was part of a systemic immunological abnormality, particularly as the activation of T_H lymphocytes reflected disease activity. What the antigenic cause of the activation is remains unknown.

Uveitis is a dynamic process, and animal models are needed to clarify the ocular and systemic events involving the T cell. In a Japanese study of experimental S antigen induced uveitis in rats[4] a rise in T_H cells in the peripheral blood was found five days after immunisation. With the onset of disease T_S cells increased, lowering the T_H/T_S ratio. In the uveal tract a T cell infiltrate appeared prior to inflammation and in the early stages more T_H than T_S cells were found. As the disease progressed T_H cells decreased until they could be identified only with difficulty in the late stages. This experiment suggests that T_H cells initiate the inflammatory response and that this is then controlled by T_S cells.

Further evidence of the influence of T cells in a similar animal model comes from an elegant study[5] from the NIH where T_H lymphocytes specifically sensitised to retinal S antigen were obtained from rats. When these cells were transferred to non-immunised rats they developed uveitis (in the absence of systemic antibody formation to S antigen) with a shorter latent period than that induced by active immunisation. Intravitreal injection produced uveitis in that eye with fewer cells than required for systemic transfer, presumably suggesting that the specific T_H cell must reach the eye to initiate the disease process. In a similar experiment T_S cells were found to downgrade the experimental uveitis, suggesting these cells can modulate the inflammatory process.

In summary a great deal is becoming known about posterior uveitis in rats, but the understanding of human disease is only just beginning.

D J SPALTON

References

1 McGuigan LE, Prendergast JK, Geczy AF, Edmonds JP, Bashi HV. Significance of non-pathogenic cross reactive bowel flora in patients with ankylosing spondylitis. *Ann Rheum Dis* 1986; 45: 566–71.

2 Jakobiec F, Marboe C, Knowles DM, Iwamoto T, Harriston W. Human sympathetic ophthalmia. An analysis of the inflammatory infiltrates by hybridomamonoclonal antibodies, immunodensity and correlative electron microscopy. *Ophthalmology* 1983; 90: 76–95.

3 Dumonde DC, Kasp-Grochoasker E, Graham F, *et al.* Antiretinal autoimmunity and circulating immune complexes in patients with retinal vasculitis. *Lancet* 1982; ii: 787–92.

4 Abrahams IW, Gregerson DS. Longitudinal study of serum antibody responses to retinal antigens in acute ocular toxoplasmosis. *Am J Ophthalmol* 1982; 93: 224–31.

5 Nussenblatt RB, Salinas-Carmona M, Leake W, Scher I. T lymphocyte subsets in uveitis. *Am J Ophthalmol* 1983; 95: 614–21.

6 Usui M, Takamara K, Shima Y, Mitsubashi M, Matsushima T. Lymphocyte subsets in experimental anatomic uveoretinitis. *Proceedings of the 4th Intrernational Symposium of Immunology and Immunopathology of the Eye.* In press.

7 Caspi RR, Roberge FG, McAllister CG, *et al.* Induction and regulation of experimental anatomic uveoretinitis in the rat. *Proceedings of the 4th International Symposium of Immunology and Immunopathology of the Eye.* In press. 1986.

British Journal of Ophthalmology, 1988, 72, 83–87

Activated T lymphocytes in uveitis

JEAN DESCHÊNES, DEVRON H CHAR, AND SHAWNYA KALETA

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SUMMARY Two colour flow cytometry techniques were used to assess the activation stages of peripheral and intraocular T lymphocytes in uveitis. Increased numbers of T lymphocytes bearing the interleukin-2 (IL-2) receptors were found in intraocular fluids or peripheral blood or both of 35/51 patients with uveitis. This increased expression of IL-2 receptors on lymphocytes correlated with increased expression of other early T lymphocyte activation markers, HLA-DR and L-35. Both T helper cells (Leu-3A+) and suppressor cells (Leu 2A+) were activated in vivo. A positive correlation was seen between lymphocyte activation and clinical uveitis activity. In idiopathic uveitis activation of Leu-3A lymphocytes (helper/inducer) was significantly increased, and intraocular activation of the Leu-2A lymphocytes (cytotoxic/suppressor) was significantly decreased. These data show that some patients with idiopathic uveitis have a perturbation of T helper cells. Twenty-two of 31 patients with idiopathic uveitis, not associated with systemic disease, had increased peripheral T lymphocyte activation. This finding indicates that in some inflammations believed to be restricted to the eye an abnormal systemic immune activation exists.

Immunological abnormalities important in the pathogenesis and pathophysiology of uveitis are poorly defined.[1] We and others have used flow cytometry to characterise the nature of intraocular lymphocyte subpopulations in uveitis patients.[2-4] The role of intraocular lymphocytes in uveitis is not clear. We have previously shown that many intraocular lymphocytes are present secondary to blood ocular barrier breakdown.[4] However, whether these cells are passive, or actively involved in the pathophysiology of the disease, is uncertain.

Newer techniques can be used to distinguish activated lymphocytes capable of mediating immunological events from resting T cells. Activation of human T lymphocytes results in the expression of interleukin-2 receptors and HLA-DR on their surfaces; these antigens are present in minute quantities on resting T cells.[5-8] In some immunologically mediated diseases activated T cells are markedly increased at the site of inflammation.[8 9] In both rheumatoid arthritis and spondylitis significantly more activated T cells are present in synovium than in the blood.[8] In multiple sclerosis an increase of activated T cells in the peripheral blood is consistent with systemic immune activation.[9]

In this study we examined uveitis patients with known systemic syndromes or idiopathic intraocular inflammation for the presence of interleukin-2 receptors and other early activation markers on T cells from intraocular fluids and peripheral blood. These studies were performed to determine the frequency of in-vivo T lymphocyte activation in uveitis and its correlation with disease activity.

Subjects and methods

Patients were examined and studied in the Uveitis Survey Unit of the Francis I Proctor Foundation. Ocular diagnoses were made on the basis of history, clinical examination, and routine laboratory tests. A diagnosis of idiopathic uveitis was made in the absence of a known clinical uveitis syndrome, systemic disease, or laboratory abnormalities. The diagnosis of HLA-B27 related uveitis was made in anterior uveitis patients who were HLA-B27 positive.

The severity of inflammation was graded by summing numerical values assigned to the various clinical factors of uveitis[10 11]: anterior chamber cells and flare (0 to 4), keratic precipitates (0 or 1), vitreous reaction (0 to 4), cystoid macular oedema, optic nerve oedema, and vasculitis (0 to 4).

Aqueous and vitreous specimens were obtained as previously described after informed consent was

Correspondence to Devron H Char, MD, Ocular Oncology Unit, Science 315, University of California, San Francisco CA94143, USA.

received.[4] Peripheral blood lymphocytes (PBLs) were partially purified with Ficoll-Hypaque density gradient (Pharmacia, Piscataway, NJ). PBLs were washed twice with cold phosphate buffered saline (PBS). Vitreous samples were filtered through nylon mesh before analysis. Cell counts were performed before and after filtration to ensure adequate recovery of lymphocytes. One million PBLs were placed in ten 12×75 mm plastic tubes (Falcon, Oxnard, CA), vitreous cells were distributed in seven 12×75 mm BSA coated plastic tubes (Falcon, Oxnard, CA), and aqueous cells were distributed in seven 400 µl BSA coated Eppendorf microtubes (Brinkman Instruments, Inc.). Cells were washed once with PBS containing bovine serum albumin 1%, sodium azide 0·1%, and heparin 1 unit/ml (staining buffer) and labelled in a volume of approximately 35 µl at 4° C for 30 minutes.

Cytofluorometric analyses of cell populations were performed in two colours with fluorescein isothiocyanate (FITC) or phycoerythrin (PE) conjugated commercial monoclonal antibodies to human leucocyte antigens (a gift from Becton Dickinson Corporation). Antibodies selected were: Leu-2A (FITC) (T cytotoxic/suppressor), Leu-3A (FITC) (T helper/inducer), Leu 4 (FITC) (T cells mitogenic), Leu-12 (FITC) (B cells), Leu-15 (PE) (T suppressor cells, NK cells, monocytes, granulocytes), anti-interleukin-2 receptors (PE), anti-HLA-DR (PE), and two experimental early activation markers for T lymphocytes L-35 and L-36 (unpublished data from Becton Dickinson Corporation). Background fluorescence activity was determined with non-specific immunoglobulins G_1 (FITC) and G_2 (PE).

Exclusion of small monocytes from the isolated lymphocytes population was verified with Leu-M3 (macrophages). Dilutions of monoclonal antibodies were 1:5 for PBLs and 1:50 for intraocular lymphocytes.[3]

Cells and antibodies were incubated for 30 minutes, at 4° C, washed, and resuspended in 30 µl of staining buffer. Fixation was obtained by addition of 30 µl of a fresh 1% paraformaldehyde solution in PBS. Samples were analysed with a dual channel fluorescence activated cell sorter (FACS IV) (Becton Dickinson Corporation). Wide angle forward light scatter, volume, green fluorescence (FITC), and red fluorescence (PE) were measured and analysed in list mode. Volume and scatter were set on the lymphocyte peak. The amplification of the red and green photomultiplier tubes was adjusted so that signals generated from the FITC positive cells did not appear over background in the red detection system and vice versa for the PE positive cells. Non-specific fluorescence (red, green, or both) in the control samples was subtracted from values for red, green or dual fluorescence in the positive samples. The percentage of activated T cells was calculated by dividing the number of activated T cells by the total number of that respective T lymphocyte total subset population.

STATISTICAL ANALYSIS

Correlations between clinical uveitis activity, steroid treatment, and intraocular and peripheral blood lymphocyte activation were calculated by Kendall's τ B statistical analysis.[12] This particular test was chosen because it can accommodate the fact that ocular samples were not obtained from patients with mild disease. Tukey's range test was used to calculate p values between lymphocyte activation in normal controls and uveitis patients.

Results

Intraocular and/or peripheral blood lymphocytes were analysed in 51 uveitis patients. Peripheral blood lymphocytes were analysed in 14 control volunteers. Fig. 1 shows a representative two-colour fluorescence histogram of IL-2 receptor and Leu-4 staining. Similar histograms were obtained with other antibodies. Each analysis was done on 500000 cells for PBLs and at least on 1000 cells for ocular samples. Table 1 shows the percentage of IL-2 positive cells in patients with uveitis. Normal control peripheral

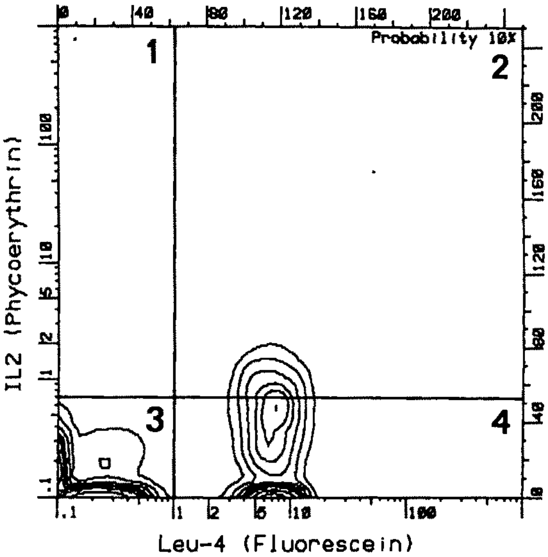

Fig. 1 *Two-colour histogram of IL-2 receptor and Leu-4 staining. Cells in quadrant 2 are Leu-4+ IL-2+; these cells are activated T cells. Cells in quadrant 3 are Leu 4− IL-2−, and therefore are non-activated lymphocytes of non-T cell lineage. Cells in quadrant 4 are Leu-4+ IL-2−, which are non-activated T cells.*

Table 1 *Percentage of aqueous (AQ), vitreous (VI), and peripheral blood (PB) IL-2 (+) T lymphocytes*

Diagnosis	*Uveitis clinical intensity*		*% IL-2 + lymphocytes*		
			2a	*3a*	*4*
Sarcoidosis	12	AQ	100·0	91·0	86·0
		PB	97·5	70·8	97·2
Pars planitis	10	PB	0·5	4·9	4·0
Toxoplasmosis	9	AQ	7·9	5·6	3·4
		PB	8·1	4·0	4·9
Idiopathic ant. uveitis	8	PB	0	2·5	2·2
Idiopathic panuveitis	8	VI	0	0	0
		PB	1·8	0·1	1·1
Pars planitis	7	PB	0·8	2·7	3·7
HLA-B27 iridocyclitis	7	AQ	9·7	9·0	5·7
		PB	2·6	5·0	1·6
Bilateral idiopathic retinal necrosis	7	VI	14·3	16·6	11·1
Idiopathic ant. uveitis	7	AQ	—	22·0	13·0
		PB	0·8	3·1	2·6
Eales' disease	6	PB	6·6	6·1	3·2
Idiopathic panuveitis	6	PB	9·2	3·1	2·6
Idiopathic panuveitis	6	PB	4·8	7·3	4·5
Idiopathic post. uveitis	6	VI	29·6	34·8	14·3
		PB	3·3	6·5	5·8
Idiopathic post. uveitis	6	VI	62·4	56·5	22·6
		PB	4·0	8·5	6·3
Idiopathic panuveitis	5	AQ	1·4	1·3	2·0
		PB	0	8·8	0
Syphilis	5	VI	2·2	58·6	24·0
		PB	0	0	0
Idiopathic panuveitis	5	PB	4·5	8·7	6·5
Fuchs's heterochromic cyclitis	5	PB	0·2	4·7	2·6
Pars planitis	5	PB	7·6	7·1	3·0
Idiopathic panuveitis	5	PB	2·1	7·4	4·0
Sarcoidosis	5	PB	44·7	13·8	10·5
Idiopathic panuveitis	5	AQ	—	—	34·8
		VI	—	0	0
		PB	5·3	9·5	7·5
HLA-B27 iridocyclitis	5	AQ	—	14·7	9·8
		PB	4·0	16·3	12·9
Idiopathic post. uveitis	4	VI	9·0	12·0	8·0
		PB	4·4	5·0	4·8
Idiopathic panuveitis	4	AQ	1·0	0	1·0
		PB	5·5	4·7	4·5
Idiopathic panuveitis	4	AQ	—	39·1	12·6
		PB	3·6	4·3	2·7
Pars planitis	4	AQ	—	35·7	19·6
		PB	0·7	7·0	5·7
Beçhet's syndrome	4	AQ	—	—	26·2
		PB	2·9	12·1	8·4
Sarcoidosis	4	PB	7·4	14·4	14·0
Iridocyclitis ankylosing spondylitis	4	AQ	—	—	15·2
		PB	9·7	8·4	7·2
Toxoplasmosis	4	AQ	—	22·6	25·2
		PB	3·6	3·3	6·0
HLA-B27 iridocyclitis	4	AQ	31·3	11·5	12·9
		PB	14·8	6·5	25·7
HLA-B27 iridocyclitis	4	PB	0	0	0
Idiopathic iridocyclitis	4	PB	4·0	6·1	3·9
Reiter's	3	PB	3·9	4·7	3·2
HLA-B27 iridocyclitis	3	PB	0·8	1·4	1·3
Pars planitis	3	PB	7·5	6·0	3·0
Idiopathic post. uveitis	3	VI	0	0	0
		PB	0	0	0
Idiopathic post. uveitis	3	PB	1·6	2·5	2·9
Idiopathic panuveitis	3	PB	0	1·7	4·3
Pars planitis	3	PB	1·6	3·5	1·8
Uveal effusion	2	PB	0·3	5·4	4·8
Birdshot choroidopathy	1	AQ	0	4·3	0
		PB	0	3·4	1·2
Idiopathic iridocyclitis	1	PB	1·2	0·6	0·7
Idiopathic panuveitis	1	PB	2·6	21·3	16·5
Idiopathic panuveitis	1	PB	0	0	0·3
HLA-B27 iridocyclitis	1	PB	0	0	1·9
Sarcoidosis	1	PB	5·3	4·4	3·6
Pars planitis	1	PB	4·5	6·7	1·9
Pars planitis	1	PB	2·4	3·2	2·1

blood T cell IL-2 receptor, HLA-DR, L-35, and L-36 expressions are shown in Table 2.

Uveitis patients had significantly more activated T cells (IL-2R positive) in the blood than healthy controls ($p<0·05$). Thirteen of 17 patients with systemic uveitis syndromes and 22 of 31 patients with idiopathic uveitis had increased IL-2R expression on Leu-4+ cells (Fig. 2).

The majority of cells in aqueous and vitreous of uveitis patients were T cells. Table 3 enumerates the total T, total B, and T cell subsets in both the intraocular components and peripheral blood in uveitis patients.

Using a Kendal τ B analysis we found a statistically significant correlation between clinical uveitis activity and the percentage of activated T cells in both intraocular fluids and peripheral blood (Table 4). A positive correlation was seen between aqueous T lymphocyte activation and peripheral blood T lymphocyte activation (Leu-2A correlation=0·714;

Table 2 *Control population*

Lymphocyte surface antigens	*% IL-2 +*	*HLA-DR +*	*L-35 +*	*L-36 +*
2A	0·6±1·1	6·7±4·4	0·8±0·4	0·9±0·4
3A	0·7±0·9	4·0±1·7	0·5±0·2	0·5±0·2
4A	1·8±1·3	ND	ND	ND

ND=not done.
± is followed by standard deviation.

p=0·0057, Leu-3A correlation=0·473, p=0·029). No correlation was seen between intravitreal T lymphocyte activation and peripheral blood T lymphocyte activation.

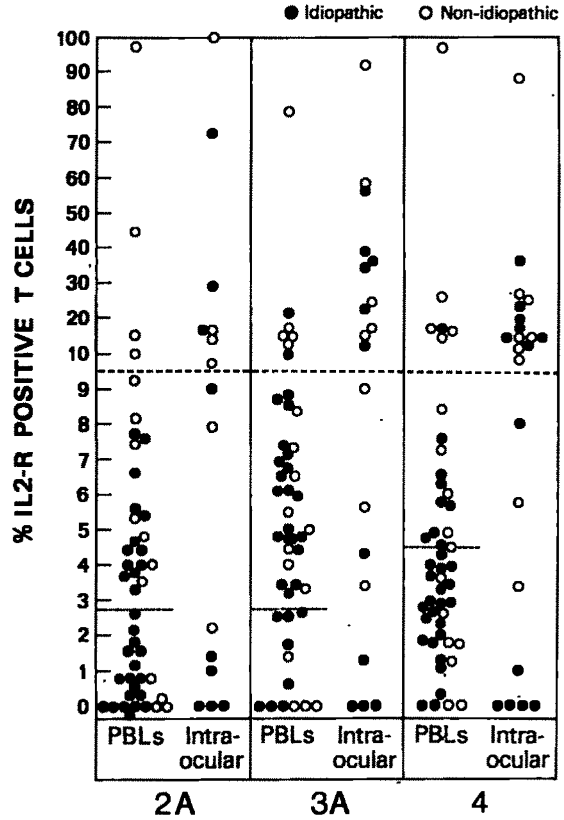

Fig. 2 *Percentage of activated T cell subsets in uveitis patients. The dotted lines represent 2 standard deviations above the mean percentage of activated T cells in controls.*

Table 3 *Uveitis patients: aqueous (AQ), vitreous (VI), and peripheral blood (PB) lymphocyte surface antigens*

	2AQ		3AQ		4AQ
(AQ)	32·2±22·7	(AQ)	36·8±21·5	(AQ)	46·6±25·5
(VI)	20·5±21·3	(VI)	18·3±20·1	(VI)	31·9±29·4
(PB)	28·3±10·6	(PB)	43·5±11·7	(PB)	72·0±11·3
	12		15		
(AQ)	8·6±7·8	(AQ)	3·2± 3·5		
(VI)	2·9±3·3	(VI)	9·6±11·8		
(PB)	7·2±6·0	(PB)	18·2±16·3		

Table 4 *Kendall's τ B correlation between uveitis clinical activity and the percentage of IL-2 (+) lymphocyte subsets*

Subsets	*Coefficients*	*Probability*
Intraocular Leu-2A	0·569	P=0·003
Intraocular Leu-3A	0·573	P=0·009
Intraocular Leu-4	0·542	P=0·014
Peripheral Leu-2A	0·269	P=0·009
Peripheral Leu-3A	0·370	P=0·0003
Peripheral Leu-4	0·275	P=0·006

Increased expression of the other early activation markers correlated well with increased expression of IL-2 receptors on T lymphocytes (HLA-DR: correlation=0·412, p=0·0008; L-35: correlation=0·567; L-36: correlation=0·411, p=0·0024) (Table 4).

The diagnosis of idiopathic uveitis correlated with increased expression of the IL-2 receptors on peripheral Leu-3A+ lymphocytes (correlation=0·247, p=0·033). No correlation was seen between increased IL-2 receptors expression on peripheral Leu-2A+ lymphocytes (correlation=0·08, p=0·5) and the diagnosis of idiopathic uveitis; a negative correlation was seen between increased IL2+Leu 2A lymphocytes in aqueous and the diagnosis of idiopathic uveitis (correlation: −0·572, p=0·049).

Discussion

We demonstrated activated T cells in aqueous, vitreous, and peripheral blood of uveitis patients using an anti-interleukin-2 receptor monoclonal antibody. Expression of IL-2 receptors on lymphocytes correlated with the expression of other early activation markers: HLA-DR, L-35, and L-36. The degree of T cell activation correlated with clinical uveitis activity.

In peripheral blood both patients with systemic syndromes associated with intraocular inflammation and patients with idiopathic uveitis had significantly more activated T cells than healthy controls. These data show systemic T cell activation in at least a subset of idiopathic uveitis patients.

We and others have previously found evidence of systemic immune response in some idiopathic uveitis patients. Kauhn *et al.*[13] found elevated systemic immunoglobulin levels in idiopathic uveitis, and we have observed that some patients have circulatory immune complexes.[14] Nussenblatt *et al.*[15] reported increased OKT8+ (suppressor cells) T lymphocytes in patients with active posterior uveitis. Snyder *et al.*[16] found elevated levels of IgG and antiganglioside antibodies in pars planitis. Murray and Rahi[17] demonstrated systemic deficits of suppressor cells in various ophthalmological conditions, including idiopathic uveitis.

Our findings suggest that some idiopathic uveitis may be systemic diseases with mainly ocular signs and symptoms. The aetiology for systemic lymphocyte activation in ocular inflammatory disease is uncertain. Lymphocytes could be activated locally, and the systemic lymphocyte activation observed might represent spillover from the eye. However, it seems improbable that a small organ like the eye would be able to generate the amount of activated lymphocytes seen in the systemic circulation. Probably this perturbation of the immune system is due either to an abnormality of immunoregulatory homoeostasis or to altered immunological reactivity towards uveogenic antigens. Our findings indicate that a perturbation of the systemic T helper cells is present in some patients suffering from idiopathic uveitis. Recently, Caspi and coworkers established a uveogenic T helper lymphocyte line capable of transferring experimental autoimmune uveoretinitis (EAU) in the rat.[18] With regard to these findings it is tempting to postulate that some idiopathic uveitis could be a 'T helper mediated disorder'. Further studies are necessary to delineate the relative importance of these mechanisms as well as to determine the relative contribution of intraocular versus systemic lymphocyte activation in uveitis.

This work was supported in part by an unrestricted grant from That Man May See, by an unrestricted grant from the Beal Foundation, and by NIH grant EY0 3675. Dr Deschênes is the recipient of a McLaughlin fellowship.

References

1 Char DH. *Immunology of ocular tumors.* New York: Grune and Stratton, 1978.

2 Kaplan HJ, Waldrep CJ, Nicholson JK, Gordon D. Immunologic analysis of intraocular mononuclear cell infiltrates in uveitis. *Arch Ophthalmol* 1984; **102:** 572–5.

3 Freeman WR, Char DH, Garovoy MR, Lyon H. Microtechniques for flow cytometric analysis of aqueous humor lymphocytes. *J Immunol Methods* 1984; **73:** 447–55.

4 Deschênes J, Freeman W, Char DH, Garovoy MR. Lymphocyte subpopulations in uveitis. *Arch Ophthalmol* 1986; **104:** 233–6.

5 Ucehiyama T, Broder S, Waldman TA. A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human T cells. I. Production of anti-Tac monoclonal antibody and distribution of Tac (+) cells. *J Immunol* 1981; **126:** 1393–7.

6 Leonard WJ, Depper IU, Ucehiyama T, Smith A, Waldman TA, Greene WC. A monoclonal antibody that appears to recognize the receptor for human T-cell growth factor; partial characterization of the receptor. *Nature* 1982; **300:** 267–9:

7 Miyawaki T, Yachie A, Uwadana N, Ohziki S, Najaoki T, Tarijuchi N. Functional significance of Tac antigen expressed on activated human T lymphocytes: Tac antigen interacts with T cell growth factor in cellular proliferation. *J Immunol* 1981; **129:** 2474–8.

8 Burmester GR, Jahn B, Gramatzki M, Zacher J, Kalden JR. Activated T cells in vivo and in vitro: divergence in expression of Tac and Ia antigens in the non-blastoid small T cells of inflammation and normal T cells activated in vitro. *J Immunol* 1984; **133:** 1230–4.

9 Hayler DA, Fox DA, Manning ME, Schlossman SF, Reinherz EL, Weimer HL. In vivo activated T lymphocytes in the peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *N Engl J Med* 1985; **312:** 1405–11.

10 Hogan MJ, Kimura SF, Thygeson P. Signs and symptoms of uveitis. *Am J Ophthalmol* 1959; **47:** 155–70.

11 Kimura SJ, Thygeson P, Hogan MJ. Signs and symptoms of uveitis II. Classification of the posterior manifestations of uveitis. *Am J Ophthalmol* 1959; **47:** 171–6.

12 Kendall MG. *Rank correlation methods.* 2nd ed. London: Griffin, 1955.

13 Kauhn LS, Schlaegel TF, Weber JC, Biegel A. Serum immunoglobulins and uveitis. *Arch Ophthalmol* 1983; **101:** 458–9.

14 Char DH, Christensen M, Stein P, Massi R. Immune complexes in uveitis. *Am J Ophthalmol* 1979; **87:** 678–81.

15 Nussenblatt RB, Salinas-Carmona M, Leake W, Scher I. T lymphocyte subsets in uveitis. *Am J Ophthalmol* 1983; **95:** 614–21.

16 Snyder DS, Tessler HH, Yokoyama MM. Immunologic studies on Voyt-Koyanagi-Harada syndrome and pars planitis. In: Silverstein AM, O'Connor GR, eds. *Immunology and immunopathology of the eye.* New York: Masson, 1979: 71.

17 Murray PI, Rahi A. New concepts in the control of ocular inflammation. *Trans Ophthalmol Soc UK* 1985; **104:** 152–8.

18 Caspi RR, Roberge FG, McAllister CG, El-Saied M, Kuwabara T, Gery I, Hanna E, Nussenblat RB. T cell lines mediating experimental uveoretinitis (EAU) in the rat. *J Immunol* 1986; **136:** 928–33.

Accepted for publication 15 December 1986.

British Journal of Ophthalmology, 1988, 72, 88–96

Experimental posterior uveitis. II. Electroretinographic studies

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SUMMARY Experimental posterior uveitis was induced by the inoculation of retinal S-antigen into black hooded Lister rats. The time course of the disease was monitored by electroretinography (ERG), and the ERG changes were correlated with clinical signs and underlying pathological damage. The ERG became supernormal in the third week after inoculation, with some loss of temporal resolution (lowered ERG flicker fusion frequency), though the disease was not clinically manifest at this time and histological examination was normal. The ERG became subnormal after 21 days as clinical signs of disease began to appear. This subnormality was associated with focal photoreceptor necrosis, the degree of destruction being proportional to the reduction in the ERG. The ERG recovered with resolution of disease in most cases, though return to control values was uncommon. We suggest that the initial supernormal ERG reflects an underlying biochemical change mediated by the action of anti retinal S-antigen antibodies.

The electroretinogram (ERG) is widely accepted as a useful clinical and experimental technique for the investigation of retinal disease. The ERG is the synchronous and sequential response of the retina to a light stimulus,[1] and analysis of the component waves allows anatomical localisation of disease processes.[2 3] The ERG has been used in the study of patients with posterior uveitis,[4-9] and both supernormal and subnormal responses of components of the ERG (usually the b-wave) have been detected. However, although these abnormalities correlated with the extent of disease observed clinically, comparative analysis with the underlying histopathology has been impossible owing to the lack of suitable material. Experimental models of disease are thus required.

Early ERG studies of experimental allergic uveitis (EAU) involved the intravitreal injection of heterologous antigen,[10-12] but recently the disease has been induced by the injection of antigen at a site remote from the eye, thus avoiding this manipulation.[13-15] The earliest electrophysiological sign of disease in rodents, which have rod dominant retinae, was an increase in the size of the scotopic b-wave, followed by a reduction and then extinction of the ERG as the disease progressed. In cone rich retinae, such as that found in the pigeon, no change was found in the b-wave, but the a-wave and oscillatory potentials became progressively reduced during active disease.[10] The subnormality of the ERG corresponded to histologically documented destruction of the retinae in all these experimental models.

We investigated the electrophysiological responses of the black hooded Lister rat with inflammatory eye disease induced by a footpad injection of retinal S-antigen.[16] Disease in this animal model is confined to the posterior segment of the eye and shows striking clinical similarities to posterior uveitis in man, especially idiopathic retinal vasculitis.[17] There is little concomitant vitreous inflammation, and artefacts induced by clouding of the media are largely avoided. The aims of this study were to correlate ERG changes during disease with the underlying pathology and to try to delineate early electrophysiological markers that might predict disease onset.

Materials and methods

GENERAL EXPERIMENTAL PROCEDURE

A total of 39 male black hooded Lister rats (Bantin and Kingman), weighing 250–300 g were used. Twenty-eight of these were experimental animals and 11 served as controls. At the age of 10 weeks

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experimental animals received 50 μg of retinal S-antigen emulsified in Freund's complete adjuvant (FCA) enriched with *Myobacterium tuberculosis* (3 mg ml^{-1}) divided into 0·1 ml aliquots given into each hind footpad. Control animals received 0·1 ml of phosphate buffered saline (PBS) and FCA. The details of the procedure to purify the retinal S-antigen by means of size and hydrophobic absorption chromatography have been described elsewhere.[18] The material used was 80% pure as assessed by sodium dodecyl sulphate gel electrophoresis (SDS-PAGE) and scanning densitometry. All rats were kept on the same shelf under 12-hour light (60 cd m^{-2})/dark cycles. They were fed with water and R and M No. 1 maintenance cubes (SDS).

The animals were divided into three groups: In each group experimental and control animals were weight matched. ERGs were performed at the same time of day for each animal.

Group I. Three experimental and three control animals were used. Each animal had an ERG recorded every two to four days (11 separate recordings/animal) until day 37 after inoculation, when the experiment was terminated.

Group II. Nine experimental animals and four controls were used. ERGs were recorded daily from day 13 to day 20 after inoculation. Experimental animals were killed when their ERG became significantly enhanced as compared with controls. Control animals were killed on day 20 after inoculation.

Group III. A: Five experimental animals had ERG recordings 120 days after inoculation and were then killed. B: Eleven experimental animals and four controls had ERG recordings every 20 days until day 86 after inoculation, when they were killed.

PROCEDURE FOR ELECTRORETINOGRAPHIC INVESTIGATION

Before each ERG recording all the animals were dark adapted for 30 minutes and anaesthetised with an intraperitoneal injection of ketamine hydrochloride (Ketalar, Parke Davis) 120–180 mg kg^{-1}, which provided a suitable level of anaesthesia for recordings to be made.[19] The animals were placed in a home built stereotaxic rat holder.

ERGs were recorded with silver electrodes embedded in a Perspex contact lens with an indifferent needle electrode placed in the skin of the cheek. The pupils were dilated with 1% tropicamide hydrochloride (Smith and Nephew). The responses from each eye were amplified (Electromed AC 3543, band width 0·2–100 Hz) and displayed on a twin channel curvilinear pen recorder (Electromed MX212). Oscillatory potentials were recorded by passing the signal through a 100 Hz high pass passive filter, and increasing the top cut to 1000 Hz.

A xenon flash bulb (Nore Microwave NV 615) projected into a dome producing ganzfeld stimulation (maximum intensity at 0·0 log units=2800 cd m^{-2}) was used to evoke ERGs. Intensity and wavelength of the flash were altered by interposing neutral density and colour (Kodak) filters. The frequency of the flash rate was varied by a function generator (Feedback TWG 500). ERGs were recorded with flashes of different intensities, beginning with the lowest (that is, with $\bar{4}$·0 log units neutral density filter). For each intensity level the stimulation rate was altered from 5 Hz to 30 Hz in 5 Hz steps. Between each change of intensity level a two-minute interval was allowed for recovery from light adaptation. After the above procedure ERGs were also recorded with red (Kodak 29) and blue (Kodak 47B) flashes. In later experiments flicker ERGs were obtained with the highest intensity flashes.

OTHER INVESTIGATIONS

After the ERG recordings each animal was assessed by slit-lamp biomicroscopy and photographs of the fundus were taken with a fundus camera (Zeiss). Fundus photography also allowed an assessment of the clarity of the ocular media by an independent observer. The recovery of all animals was monitored and all animals were weighed regularly to assess their state of health. At the end of each experimental series, the animal was anaesthetised with urethane (1·5 g kg^{-1}) and fluorescein angiography was carried out. The animals were bled by cardiac puncture, killed by cervical dislocation, and the eyes enucleated.

HISTOLOGICAL PROCEDURE

The enucleated eyes were placed in 4% glutaraldehyde for 12 hours and then in 10% neutral buffered formalin for more than 24 hours. The eyes were dehydrated through graded alcohols, cleared in toluene, and embedded in wax. Histological sections were stained with haematoxylin and eosin throughout.

Results

GROUP I: ERG CHANGES FROM DAY 3 TO 37 AFTER INOCULATION

The main features of the ERG changes observed in experimental animals in the initial study are shown in Fig. 1. In two animals (E1 and E3) the ERG became supernormal prior to the onset of disease, and this change was associated with the appearance of vitreous cells. Subsequently in these two animals the ERG values fell, becoming subnormal in E1 with the onset of clinical disease (disc swelling, periphlebitis, and retinal infiltrates), approaching subnormality in

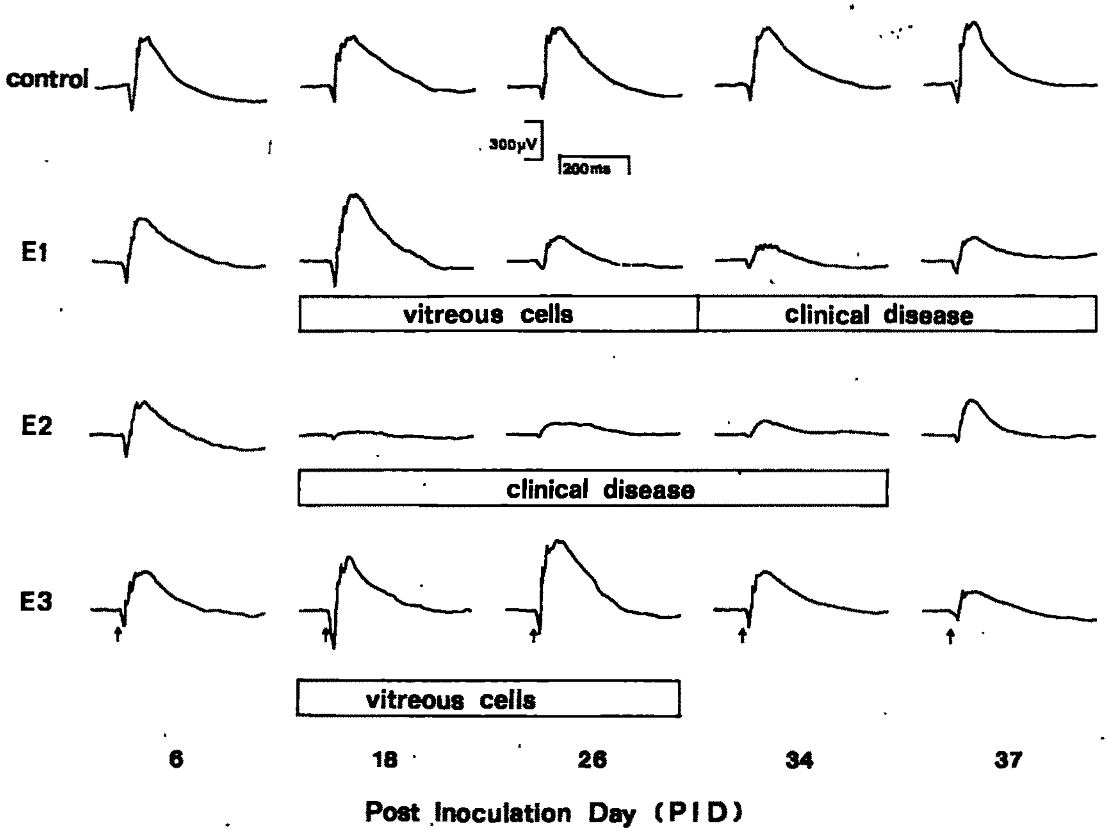


Fig. 1 *ERGs at the highest light intensity (0 log units (Lu)) for one control animal and three experimental animals (E1, E2, E3) at postinoculation days 6, 18, 26, 34, and 37. Showing the relationship between clinical disease and ERG waveform. Arrows indicate stimulus.*

E3. In animal E2 a bilateral posterior uveitis was evident on day 16, associated with a severely reduced ERG. However, in this animal the ERG recovered as disease settled, though it was still subnormal at the termination of the experiment.

A number of associated features were observed with the above ERG changes. Firstly, there was no change in the b-wave:a-wave amplitude ratio (Fig. 2) indicating that the increase or decrease in the ERG was not selective and that the lesion causing this change occurred at the level of the photoreceptor. Secondly, the oscillatory potentials (Fig. 3) changed

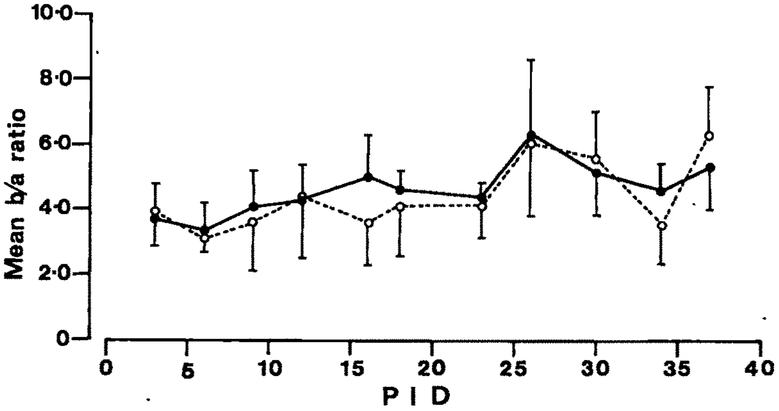


Fig. 2 *The ratio of the a- and b-waves (mean±SD) for control (solid line) and experimental (dashed line) animals at days after inoculation.*

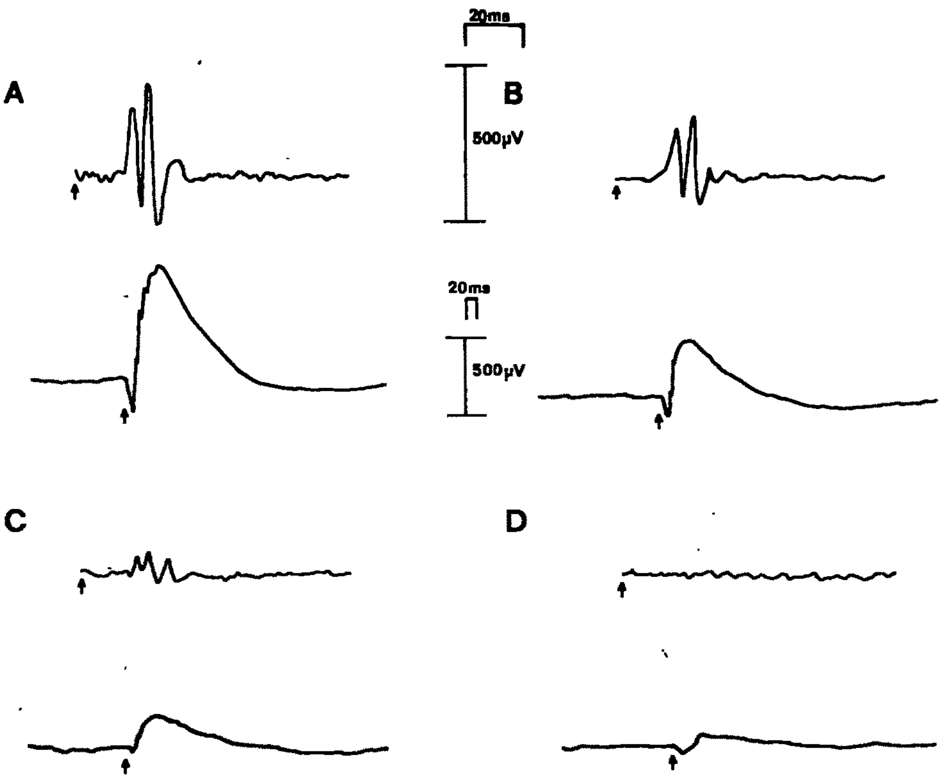


Fig. 3 *Oscillatory potentials (upper trace of each set) and corresponding ERGs (lower traces). The oscillatory potentials were recorded via a high-pass filter. From control (B) and experimental animal E3 at PID 18 (A), E1 at PID 34 (C) and E2 at PID 18 (D). Arrows indicate stimulus. Note calibration changes.*

according to the state of the whole ERG. Thus when the ERG became supernormal the oscillatory potentials increased in size, and when it was subnormal they were abolished. Thirdly, there was no change in either the a-wave or b-wave implicit times (measured from the stimulus onset to the peak of the wave) throughout the experiment (Fig. 4). Finally, the ERG flicker fusion frequency (EFFF) showed a gradual decline over the study period in experimental animals (Fig. 5). EFFF is a measure of the temporal resolution of the retina and is measured by the stimulating frequency at which the ERG wavelets became indistinguishable from the baseline.

Figs. 6A, B, C, D illustrate the histological features found in a control animal and an experimental animal (E2) at the end of the study period. The animal with active disease (E1) showed 1+ vitreous cells and an active retinal perivasculitis with some focal photo-

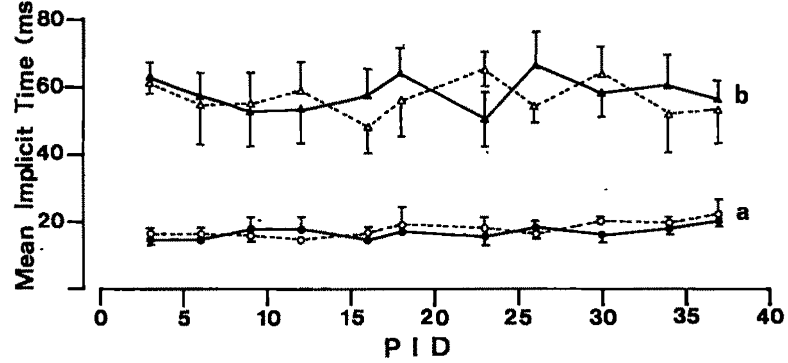


Fig. 4 *Implicit times (mean±SD) of the a-wave (circles) and b-wave (triangles) for control (solid line) and experimental animals (dashed line) at 0 Lu at days after inoculation.*

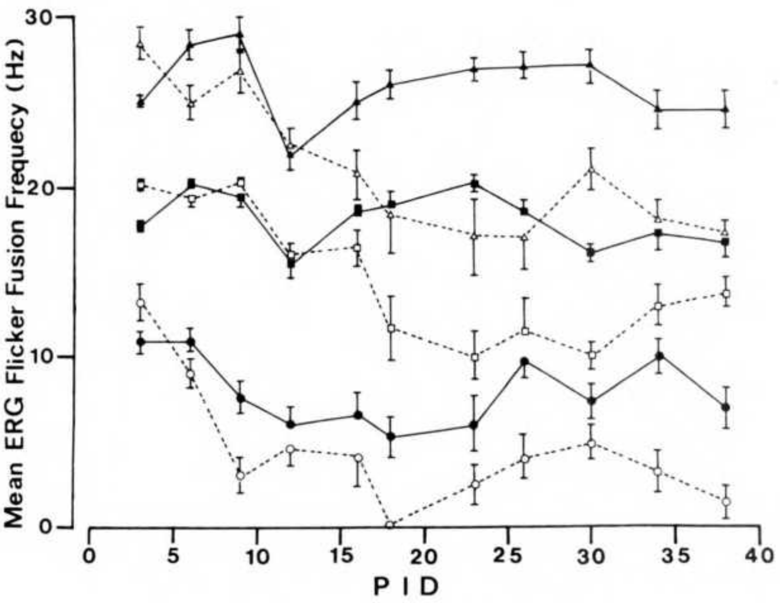


Fig. 5 *ERG flicker fusion frequency (mean±SD) for control (solid line) and experimental (dashed line) animals at 0 Lu (triangles), 2 Lu (squares), and 4 Lu (circles) at days after inoculation.*

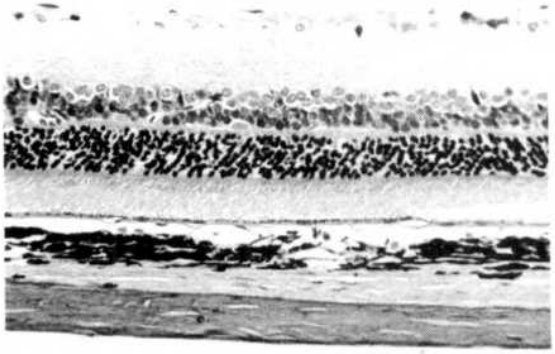


Fig. 6A

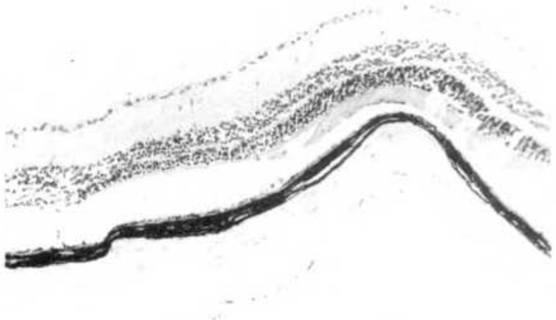


Fig. 6B

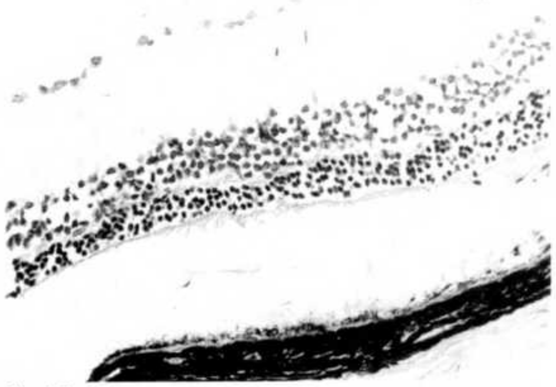


Fig. 6C

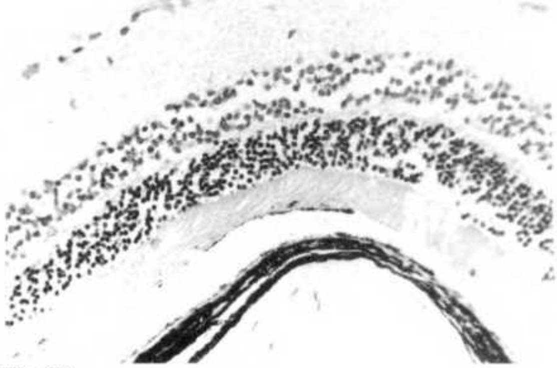


Fig. 6D

receptor loss, while the third animal (E3) showed no abnormality.

GROUP II: THE SUPERNORMAL RESPONSE – CLINICOPATHOLOGICAL CORRELATIONS

This experiment was designed to see if all animals produced a supernormal ERG prior to the onset of disease and whether this correlated with any underlying pathological features. ERGs were recorded on a daily basis from day 13 after inoculation, and each animal was killed when the ERG became supernormal. A supernormal ERG was defined as that showing larger b-wave amplitudes than controls at all intensity levels with 95% confidence limits. It was found that all animals' ERGs went through this stage, with a peak incidence on day 15 (Fig. 7). Again, the appearance of a supernormal ERG was associated with enhanced oscillatory potentials but a reduction in EFFF.

Histological examination of the eyes in which the ERG became supernormal was performed so that the examiner did not know the results of the ERGs. No abnormalities of the retina were found, and, although significant numbers of vitreous cells were found in some eyes, no correlation could be made between this number and the degree of supernormality of the ERG.

GROUP III: THE SUBNORMAL RESPONSE AND RECOVERY

Two groups of animals were used to assess the subnormal ERG and its subsequent recovery. In the first group of five animals three had suffered bilateral posterior uveitis by day 28 after inoculation and their ERGs were extinct at 120 days. In the other two animals, where uveitis was not observed within 28 days, the ERG was subnormal at 120 days. Histological examination of the eyes of these animals showed complete photoreceptor loss with glial replacement (Fig. 8) where the ERG was extinct, while in those where the ERG was subnormal there was focal photoreceptor destruction. The other layers of the retina, the pigment epithelium and choroid, appeared normal. There was no evidence of continuing inflammation in any eye as judged by the presence of inflammatory cells.

Fig. 6 A: *Photomicrograph of peripheral retina taken from a control animal with a normal ERG (Haematoxylin and eosin, ×200).* B: *Photomicrograph of peripheral retina taken from an animal with a subnormal ERG after disease had settled. Large areas of photoreceptor outer segment are destroyed (H and E ×100).* C: *Enlargements of the affected areas show concomitant thinning of the outer nuclear and plexiform layers, whereas* D: *there are areas of relatively normal retina (H and E). The retina is artefactually detached. Pigment epithelium and choroid appear normal (×200).*

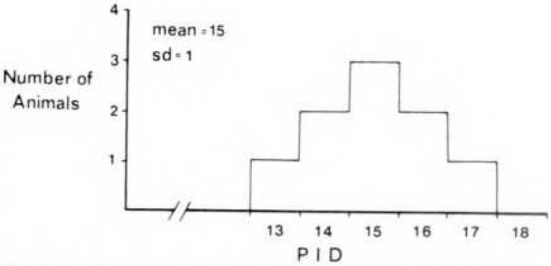


Fig. 7 *Histogram showing the number of animals that went supernormal in at least one eye for each PID.*

The subnormal response was analysed further in a group of 15 animals (10 experimental, five controls) in a longitudinal study until day 86 after inoculation. Five animals with subnormal ERGs on day 21 were killed and the remaining animals had their ERGs recorded every 20 days. Fig. 9 shows the change in the ERG b-wave amplitudes at five different light intensities for the animals that were followed up. In all experimental animals there was a significant fall in the ERG on day 21 with variable recovery after this. Thus some animals returned to control values, while others remained persistently subnormal. The subnormal ERG was also compared against control values as a function of relative log intensity of flash. Fig. 10 shows that the amplitude of the experimental animals' ERGs fell below that of the control animals at all intensities, and that the greater the intensity the greater the fall, as shown by a lower slope in ERG increase.

Discussion

We have demonstrated that there is a close correlation between the changes in ERG function and the

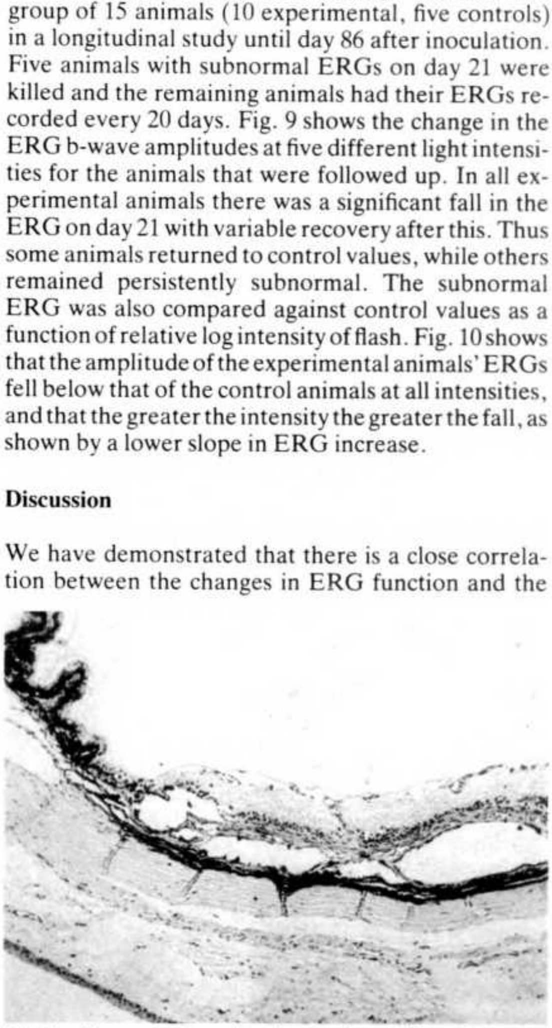


Fig. 8 *Photomicrograph to show end stage disease in a severely affected rat which had an extinct ERG. The photoreceptors are completely replaced by fibrous tissue and there is some thinning of the inner nuclear layer. H and E, ×200.*

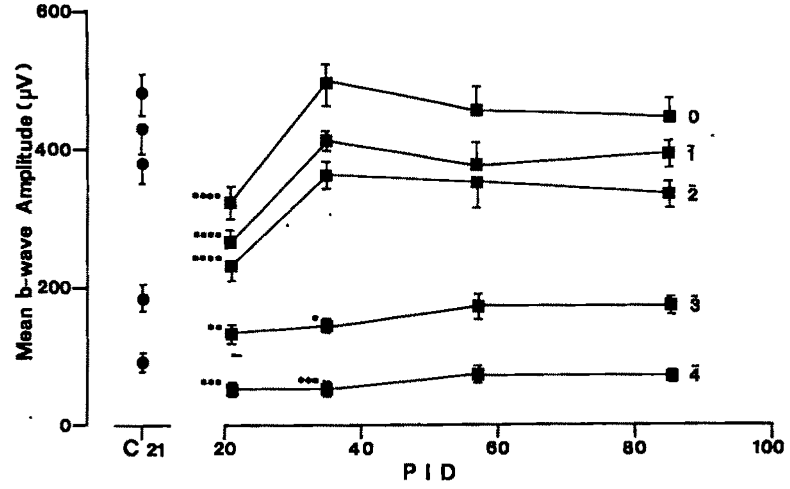


Fig. 9 b-Wave amplitude (mean±SE) for controls at PID 21 (circles) and experimental animals (squares) at PIDS 21, 37, 59, and 86 at five intensities (Lu). Student's t test compared the values of control and experimental animals. $^{****}p<0{\cdot}0005$, $^{***}p<0{\cdot}005$, $^{**}p<0{\cdot}025$, $^{*}p<0{\cdot}05$.

pathological changes of posterior uveitis in black hooded Lister rats produced by inoculation of retinal S-antigen. The ERGs underwent a supernormal stage 13–18 days after inoculation, when no pathology of the retina was evident. The ERGs then became rapidly subnormal as pathological changes developed in the photoreceptors, and recovered slowly to approach control levels with clinical recovery of the disease. The degree of subnormality of the ERG correlated with the extent of photoreceptor destruction when disease had settled. Even when clinical recovery from the disease had occurred, focal photoreceptor destruction was still apparent in histological sections of eyes from those animals which showed persistently subnormal ERGs.

The ocular inflammation induced by the inoculation of retinal S-antigen in the black hooded Lister rat primarily affected the retina. The disease produced a marked retinal vasculitis confirmed both clinically and angiographically. The retinal vasculitis was accompanied by a focal mononuclear cell infiltrate in the photoreceptor layer associated with necrosis and, in very severe disease, the whole photoreceptor layer was replaced by glial tissue. Pathological changes affecting the iris, ciliary body, and choroid were rarely seen.[17]

The physiological function of the retina underwent dynamic changes in this animal model of posterior uveitis as the ERGs initially increased before they significantly decreased. The initial increase in the ERG often coincided with the presence of inflammatory cells in the vitreous, but no clinical or histological signs of retinal disease were seen. The increase in ERG amplitudes was associated with a reduction in the ERG flicker fusion frequency, which indicated that 'supernormality' of the ERG was a transiently occurring abnormal response of the retina.

Previous authors[12 14] have also noted supernormality of the ERG in experimental uveitis and in uveitis in man,[9] the changes being most marked in the b-wave, indicating that the initial lesion may lie in the post-receptoral retina from where the b-wave is generated. Others,[20] however, have reported an increase in the ERG c-wave associated with changes on electron microscopy in the retinal pigment epithelium (RPE), suggesting that the earliest site of disease is the apical border of the pigment epithelium, where the c-wave is generated.[21] We found the amplitudes of both the a- and b-waves were increased without any change in the b:a ratio. This would suggest that the initial lesion was likely to be at the level of the photoreceptor, from which retinal S-antigen is derived.

The question arises why the ERG was supernormal before retinal disease became apparent. Since supernormality occurred in the third week after inoculation, when antibody titres reached their highest levels,[17] we suggest that the supernormal ERG is due to some unidentified biochemical change associated with the activity of antibodies against retinal S-antigen. There is now increasing evidence that retinal S-antigen is identical to the 48K protein involved in visual transduction.[22] This protein is thought to cap off phosphorylated rhodopsin to maintain it in an inactive state. Antibodies against this protein therefore may mop up the available S-antigen and in turn allow an uninhibited reaction by activated rhodopsin. However, until these antibodies have been shown to react with S-antigen in vivo, this hypothesis remains speculative.

Our study also showed that the ERGs became

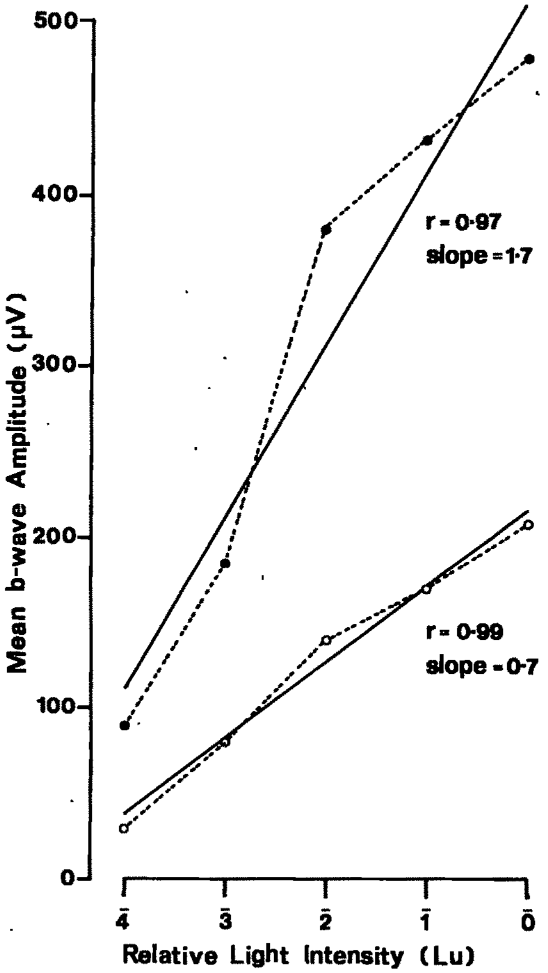


Fig. 10 *Mean b-wave amplitude for control (closed circles) and experimental animals (open circles) on PID 21. Solid lines are best fits by regression analysis at the different light intensities. r=correlation coefficient.*

subnormal during active disease, but in most cases they recovered to a varying extent when the disease had settled. The depression of the ERG has been found by other authors studying EAU,[11,12,14,15] but they noted that the change was mostly confined to the b-wave, implicating the inner retinal layers. Furthermore similar changes have been found in man.[5,6,9] This pattern of ERG change would also have been expected in this study, since the earliest sign of disease observed histologically was a perivasculitis of the retinal vessels which supply the retinal structures that generate the b-wave. However, we found that both the initial increase and subsequent depression of the ERG occurred without affecting the b:a ratio. The decrease in both a- and b-wave amplitudes of the ERG predicts that the lesion responsible affects the photoreceptor layer, and this was confirmed histologically as the main pathology in this animal model was destruction of the photoreceptors. Furthermore, two functions of the ERG predicted that this destruction was a focal rather than a diffuse process. Firstly, the implicit times of the a- and b-waves did not change, and this has been shown to correlate with focal rather than diffuse patterns of retinal disease.[23,24] Secondly, the slope of the intensity/amplitude function was reduced, suggesting a loss of functional retinal area rather than overall retinal sensitivity loss. Moreover in cases when the ERGs were extinguished a complete photoreceptor loss was apparent.

We noted that in the majority of animals the ERGs recovered after the disease had settled. The degree of this recovery ranged from none at all, when the photoreceptor layer was completely destroyed, to control values, when the photoreceptor layer was largely unaffected. This finding implies that other mechanisms induced by inflammation in the retina must contribute reversibly to the depression of the ERG during active disease. It is also important to note that the good correlation between the degree of ERG loss and the extent of photoreceptor destruction was found when the disease was inactive. On the basis of these observations we suggest that the measurement of ERG functions when the disease is inactive may play an important role in estimating the extent of photoreceptor damage in posterior uveitis.

The authors thank Professor H Ikeda for the use of her laboratories, useful discussions, and critical review of the manuscript, Mr R Dewhirst for help in preparing the illustrations, and Mrs G Blake for secretarial assistance. Retinal S-antigen was kindly provided by Dr E Kasp, Department of Immunology, St Thomas's Hospital. This work was supported in part by grants from the Medical Research Council (grant no. G 8303319 SB), the TFC Frost Charitable Trust, and the Research (Endowments) Committee, St Thomas's Hospital. JR is supported by a grant from the Special Trustees of St Thomas's Hospital to Professor H Ikeda. MRS holds a Training Awards Fellowship from the Medical Research Council.

References

1 Brown KT. The Electroretinogram: its components and their origins. *Vision Res* 1968; **8**: 633–77.
2 Tomita T, Yanagida T. Origins of the ERG waves. *Vision Res* 1981; **21**: 1703–7.
3 Ikeda H. Clinical electroretinography. In: Halliday AM, ed. *Evoked potentials and clinical testing*. London: Churchill Livingstone, 1982: 121–47.
4 Algvere P. Electroretinographic studies on posterior uveitis. *Acta Ophthalmol (Kbh)* 1967; **45**: 299–313.
5 Hatt M, Niemeyer G. Elektroretinographie bei morbus Behçet. *Graefes Arch Klin Exp Ophthalmol* 1976; **198**: 113–20.
6 Karpe G. The electroretinogram under pathological conditions. *Acta Ophthalmol (Kbh)* 1945; **24** (suppl): 69–90.
7 Straub W. *Das electroretinogramm*. Stuttgart: Enke, 1961.
8 Yonemura D, Tsuzuki K, Aoki T. Clinical importance of the oscillatory potential in the human ERG. *Acta Ophthalmol (Kbh)* 1962; **70** (suppl): 115–23.

9 François J. L'electrorétinographie dans les uvéites. *Ophthalmologica* 1953; **125:** 137–43.

10 Takata H. Electroretinographic studies on experimental uveitis. Report 1: ERG in experimental uveitis. *Nippon Ganka Gakkai Zasshi* 1963; **67:** 1814–27.

11 Algvere P, Hedin A, Kock E. The electroretinogram and histopathology in experimental uveitis of the pigeon. *Acta Ophthalmol (Kbh)* 1968; **46:** 920–35.

12 Takata H. Electroretinographic studies of experimental uveitis. Report II. Analysis of 'Inflammation type ERG'. *Nippon Ganka Gakkai Zasshi* 1963; **67:** 1829–37.

13 Lawwill T, Wacker W, Macdonald R. The role of electroretinography in evaluating posterior uveitis. *Am J Ophthalmol* 1972; **74:** 1086–93.

14 Macdonald R. Correlative studies on experimental allergic uveoretinal disease. *Trans Am Ophthalmol Soc* 1971; **69:** 397–439.

15 Wong VG, Green WR. Rhodopsin and blindness. *Trans Am Ophthalmol Soc* 1977; **75:** 272–82.

16 Wacker WB, Donoso LA, Kalsow CM, Yankeelov JA, Organisciak DT. Experimental allergic uveitis: isolation, characterisation and localisation of a soluble uveito-pathogenic antigen from bovine retina. *J Immunol* 1977; **119:** 1949–58.

17 Stanford MR, Brown EC, Kasp E, Graham EM, Sanders MD, Dumonde DC. Experimental posterior uveitis. I: Clinical, angiographic, and histopathological features. *Br J Ophthalmol* 1987; **71:** 585–92.

18 Kasp E, Banga JP, Sanders MD, Dumonde DC. A novel approach for the purification of human, porcine and bovine S-antigen utilising hydrophobic absorption chromatography. *Invest Ophthalmol Vis Sci* 1985; **26** (suppl): 97. ARVO abstracts.

19 Sasovetz D. Ketamine hydrochloride. An effective general anesthetic for use in electroretinography. *Ann Ophthalmol* 1978; **10:** 1510–4.

20 Asayama R, Yoshida E, Yano T, Ikeda K, Nagata M. Experimental studies on the significance of some components of the clinical ERG. In: François J, ed. *The clinical value of electroretinography*. ISCERG Symp. Ghent 1966. Basel: Karger, 1968: 171–83.

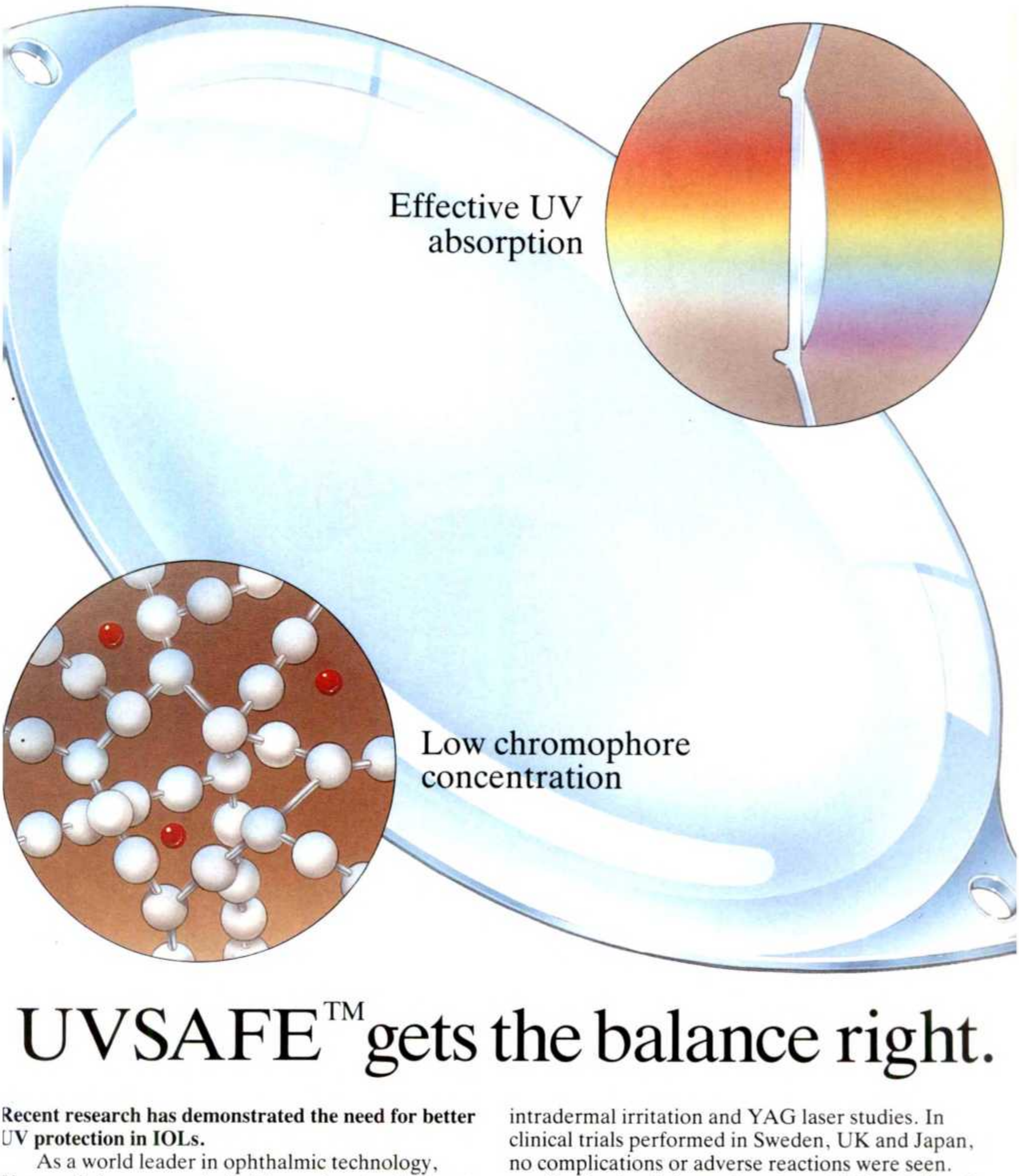
21 Brown KT, Wiesel TN. Localisation of origins of electroretinogram components by intraretinal recording of the intact cat eye. *J Physiol (Lond)* 1961; **158:** 257–80.

22 Pfister C, Chabre M, Tuyen VV, *et al.* Retinal S-antigen identified as the 48K protein regulating light-dependent phosphodiesterase in rods. *Science* 1985; **228:** 891–3.

23 Berson EL, Gouras MD, Hoff M. Temporal aspects of the electroretinogram. *Arch Ophthalmol* 1969; **81:** 207–14.

24 François J, de Rouck A. Behaviour of the ERG and EOG in localised retinal destruction by photocoagulation. In: Burian HM, Jacobson JH, eds. *Clinical electroretinography*. London: Pergamon, 1966: 191–202.

Accepted for publication 4 December 1986.



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British Journal of Ophthalmology, 1988, **72**, 97–100

On the management of retained airgun pellets: a survey of 11 orbital cases

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From the Manchester Royal Eye Hospital

SUMMARY Relevant factors determining the management of inaccessible retained lead airgun pellets are discussed in relation to 11 orbital cases. Although the injuries were of between one month's and 26 years' standing, serum lead levels were normal at under 350 μg/l in all instances. This is attributable to the modern alloy composition of the ammunition in question. It is concluded that surgical intervention may be indicated only where there is a mechanical disturbance of ocular motility allied with good visual function.

The question of whether or not surgical management of retained lead pellets is indicated has been raised recently.[1] Possible dangers of extraction in anatomically complicated regions must be weighed against the risks of leaving the foreign body in situ. In the case of the orbit these risks would indeed have to be great to justify a difficult and exacting procedure. This is particularly true where the eye retains good visual function, as operative trauma to the optic nerve or its vascular supply would be irredeemable. In the absence of impaired ocular motility, fate might well be tempted by intervention.

This study of 11 patients with retained orbital lead pellets was carried out to assess the possible risks entailed in adopting a conservative approach. Apart from possible mechanical effects resulting from such a presence, we particularly examined the hazard of lead toxicity. Chronic lead intoxication was common in ancient times. More recently its incidence has fallen dramatically. In Britain 1058 cases were reported in 1900 and 107 in 1967. The first occupational risk to come under the scrutiny of Parliament was that of lead workers in 1883 with the Factories Act.[2] In the past lead was used in the manufacture of many consumer products, though nowadays its most pervasive presence results from its addition to petrol.

The clinical picture of intoxication includes colicky abdominal pains, stomatitis with a blue line round the gums, polyneuritis with wrist drop, and encephalopathy. A microcytic anaemia with punctate basophilia is usually found.[2] Ocular complications arise in 1 to 2% of systemic cases. Papilloedema, retinal haemorrhages, and vascular sheathing may be noted, as well as pupillary dilatation and extraocular muscle palsies. Optic neuritis along with involvement of the remainder of the visual pathway is usual, and encephalopathy may be associated with cortical visual loss.[2,3] Treatment involves clearance by chelating with agents such as EDTA, dimercaprol, or penicillamine. Osmotic or surgical management of encephalopathy may be required.[3]

Materials and methods

Eleven patients with retained lead pellets in the orbit of varying duration were assessed. Ocular examination with visual result, orthoptic evaluation of eye movement where applicable, and radiological confirmation of anatomical site were carried out. Serum lead levels were measured at the National Occupational Hygiene Service Laboratories in Fallowfield, Manchester. The atomic absorption electrothermal liquid presentation method of lead level analysis was used.

Results

All patients had been shot with a typical 'narrow waisted' airgun pellet of 0·22 calibre, apart from one. Case 4 retained a copper coated lead ball. Ages at the time of injury ranged from 11 to 18 years for the males. The female in the series was 27 years old.

The duration of foreign body retention varied from one month to 26 years, being more than two years in six cases. All serum lead levels fell within the normal

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Table 1 *Summary of case reports*

Case	*Sex*	*Age*	*Duration of retention*	*Blood lead (normal <350 µg/l)*	*Eye*	*Assailant status*	*Final VA*	*Injury/action*	*Orthoptic findings*	*x-ray location of pellet*
1	M	18	26 yr	140 µg/l	R	Known	6/6	Eventual inferior retinal pigment disturbance	NAD	Posterior orbit: inferolateral extraconal
2	M	11	8 yr	170 µg/l	L	NA	NPL	Disorganised eye following perforation injury	NA	NA
3	M	15	7 yr	190 µg/l	L	Known	NPL	Disorganised eye following perforating injury. Primary repair	NAD	Apex orbit: superior
4	M	14	4 yr 5/12	110 µg/l (copper= 12·3 µmol/l)	R	With malice	6/12	Hyphaema. Inferior retinal haemorrhage. Choroid rupture	NAD	Mid-orbital: inferior intraconal
5	M	14	3 yr 7/12	80 µg/l	R	Unknown	6/4	Superior retinal commotio	NAD	Apex of orbit: superonasal
6	M	16	2 yr 5/12	120 µg/l	L	Self inflicted accident	AE	Perforating injury. Repair then enucleation	NA	Mid-orbital: superotemporal extraconal
7	M	14	2 yr	90 µg/l	L	Unknown	6/6	Superior retinal haemorrhage with commotio. Choroid rupture	NAD	Mid-orbital: superomedial extraconal
8	M	12	1 yr 3/12	290 µg/l	R	Known	AE	Perforating injury. Repair then enucleation	NA	Temporal fossa after breaching lateral orbital wall
9	F	27	1 yr 2/12	310 µg/l	L	Unknown	6/9	Medial retinal haemorrhage	Reduced left adduction, abduction and elevation	Mid-orbital: medial extraconal
10	M	17	2/12	170 µg/l	R	Known	6/6	Inferior retinal commotio	NAD	Apex of orbit: inferior
11	M	15	1/12	110 µg/l	L	With malice	6/18	Medial retinal commotio. Orbital exploration with medial rectus disinsertion	Reduced left adduction and elevation	Mid-orbital medial extraconal

VA=visual acuity. NA=not available. NAD=no abnormality detected. AE=artificial eye. NPL=no perception of light.

range of less than 350 µg/litre (Table 1), from 80 µg/l to 310 µg/l. In the case of the copper coated pellet (case 4), the serum copper level was also normal, at 12·3 µmol/l (normal range 12–20 µmol/l).

There was no preference for the eye involved, with six of the 11 cases being left sided. In five accidental incidences the assailant was known to the victim, notably in case 6, where it was the patient himself. In the other five cases in which histories were obtained three assailants were unknown and another two acted with malice. Good visual results of 6/12 or better were found in six patients. A moderate result of 6/18 was noted in a further patient. Two had no light perception, with disorganised eyes, and another two had had enucleation of their eye, with a prosthesis. In the less severe cases injuries included commotio retinae, intraretinal haemorrhage, and choroidal rupture. An unsuccessful orbital exploration which included disinsertion of the medial rectus muscle was performed in case 2.

Orthoptic studies of ocular motility in eight of nine relevant cases (excluding those two with artificial eyes) showed only two with limitation of eye movements. One of these (case 2) had undergone the exploratory procedure mentioned earlier. Radiology in 10 cases revealed three medially placed pellets, two of which were associated with orthoptic abnormalities, and two laterally placed pellets, with a third which passed through the lateral wall into the temporal fossa (case 8). Three more were located at the apex of the orbit, and finally one was found within the muscle cone.

Discussion

Reports of lead toxicity following shotgun wounds were frequent in the last and early part of this century. More recent accounts are less usual. In two series Leschke[4] and Machle[5] described six such cases. Machle[5] stressed the dangers of delayed intoxication. Rossem and Vlaardingerbroek[6] noted a severe injury, requiring later amputation of a leg, which caused acute lead intoxication in a matter of three days. Other chronic instances were recorded by Bile,[7] whose patient was successfully treated with $CaNa_2EDTA$, and Savic and Cosic,[8] who had one patient with all the laboratory findings of intoxication and another with negative findings. Fazzari and

Formiconi,[9] in their study of 17 cases, considered that the determination of urinary coproporphyrin would be useful, and agreed with Fabroni *et al.*[10] in an account of 10 further cases that lead may be absorbed as a fatty compound. Neither of these series, nor that of six cases reported by Horiuchi *et al.*,[11] included any examples of clinical intoxication, though raised levels in the blood and urine were present in some instances.

More recently Dillman *et al.*[12] described a patient who developed a full clinical picture 20 years after retaining lead shot in a hip joint. On reviewing 18 further cases these authors surmised that a bony site of injury, particularly if exposed to synovial fluid, was likely to result in significant toxicity. Prompted by the above case of acute intoxication from the Netherlands,[6] Schmidt *et al.*[13] conducted animal experiments, and were unable to demonstrate toxicity from lead pellets. They ascribed this to developments in ammunition manufacture. Previously, soft or pure lead was used without any coating, whereas current hard shot alloy includes a small percentage of antimony (Sb), making it insoluble. As well as this, coatings such as graphite or lacquer may be applied. Morl *et al.*,[14] in a survey of a wide spectrum of military injuries, confirmed that lead intoxication is not to be expected from bullets made to modern specifications. Airgun pellets these days are made with a 0·5% antimony content. No coating is normally used, though coatings such as copper, nickel, or graphite are available. A lacquer coating is undesirable because excessive hardening may render the pellet more dangerous.

In this report the pellets were of 0·22 calibre, as is usual in such injuries. The lighter 0·177 calibre favoured by enthusiasts is both more accurate and less lethal. Bowen and Magauren,[15] in a report of 105 ocular injuries from airgun pellets in Liverpool, failed to show evidence of lead toxicity in four patients selected from 16 with pellets retained in the orbit or ethmoid for between a few weeks and six years. This is in accordance with our negative findings in 11 such cases with a maximum retention of 26 years. However, a report of presumed local optic nerve toxicity from a lead pellet in the orbit was given by Dambite,[16] where treatment with unithiol improved the visual function of the eye involved.

Visual prognosis for these patients depends on whether the eye has been perforated. Even where this has not occurred the kinetic energy of the event is such that severe blunt injury to the eye may be evident. This can take the form of hyphaema, iridodialysis, traumatic cataract, commotio retinae, vitreous haemorrhage, choroidal rupture, and retinal tears or detachment. In 24% of the series of 105 cases from Liverpool[15] vision was 6/18 or worse for such reasons. The remaining patients without perforating injury (57%) retained good vision of 6/12 of better. All but one of 16 perforated eyes was lost. Sevel and Atkins[17] conducted a postal survey of 87 cases in South Africa and noted good acuity where the eye was not penetrated. Useless eyes were not necessarily enucleated in this series, with 29 having perception of light or being totally blind. In view of the risk of sympathetic ophthalmitis, noted on one occasion by Bowen and Magauran,[15] it may be more prudent to enucleate. Two patients in our report (cases 2 and 3) come into this category.

As regards the importance of possible mechanical effects, the Liverpool series included only one instance of ocular motility disorder. In that case the pellet was located at the apex of the orbit. There are two in this series, both with medially placed pellets. One of these (case 11) had exploratory surgery where the medial rectus was disinserted, and may therefore have been iatrogenic. In the other patient (case 9) the mechanism of restricted motility must remain speculative. It may result either from damage to extraocular musculature and its innervation, or else a mass effect and secondary tethering might be responsible.

Laffers and Brehm[18] advocate the removal of orbital pellets, quoting two cases with postoperative improvement in ocular motility. In one instance though, a projectile larger than an airgun pellet was found. Duke-Elder stated that[19] in the absence of definite indications an intraorbital foreign body should be left alone. Concurring with this viewpoint, Stallard[20] advised that a metallic foreign body less than 4 mm in diameter should not be removed unless there is pain, inflammation, or increasing disability. Because lead toxicity has not been found to be a complication, removal of retained orbital pellets should not be undertaken routinely. In those few cases where ocular motility is compromised and visual acuity reasonably good, recovery of the pellet can be considered.

References

1 Cudmore RE, Boothroyd A. *Lancet* 1985; i: 765–6.
2 Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1972: 14 (2): 1235–8.
3 Greenseid DZ, Leopold IH. Toxic retinopathies. In: Duane TD, ed. *Clinical ophthalmology*.. Philadelphia. Harper and Row, 1982: chapter 33: 9.
4 Leschke E. *Clinical toxicology*. London: Churchill, 1934.
5 Machle W. *JAMA* 1940; **115**: 1536.
6 Rossem C van, Vlaardingerbroek WM. Acute loodvergiftiging door een hagelschotverwonding. (Acute lead poisoning caused by shotgun pellets.) *Ned Tijdschr Geneeskd* 1965; **109**: 1110–3.
7 Bile G. Saturnismo florido da ritenzione di proiettilo. (Florid lead poisoning from retention of bullets.) *Lavoro Umano* 1969; **21**: 129–36.
8 Savic J, Cosic V. Trovanje olovom prouzrokovano zaostalim projektilom. (Lead poisoning caused by a retained bullet.) *Vojnosanit Pregl* 1966; **23**: 341–6.

9 Fazzari C, Formiconi G. L'assorbimento del piombo da proiettili ritenuti nell'organismo. (Absorption of lead from projectiles retained in the organism.) *Minerva Medicolegale* 1965; **85:** 41–5.

10 Fabroni F, Barni B, Barni I. In merito al saturnismo da ritenzione di proiettili multipli. (Lead poisoning by retention of multiple lead shot.) *Giornale de Medicina Legale, Infortunistica et Tossicologia* 1967; **12:** 382–91.

11 Horiuchi K, Horiguchi S, Utsunomiya T, *et al.* Laboratory studies on the lead poisoning in six cases with lead shot lodged in the tissues. *Osaka City Med J* 1969; **15:** 7–12.

12 Dillman RO, Crumb CK, Lidsky MJ. Lead poisoning from a gunshot wound: report of a case and review of the literature. *Am J Med* 1979; **66:** 509–14.

13 Schmidt R, Schultka R, Franzen E. Klarung der Frage nach der Bleitoxizität handelsublichen Schrotes durch histochemische und chemische Untersuchungen. (Histochemical and chemical studies on the lead toxicity of small shots in commercial usage). *Verhandlungen der Anatomischen Gesellschaft* 1969; **63:** 507–13.

14 Morl F, Schmidt R, Schultka R, Franzen E, Rautschke R. Histochemical, spectrum analytic, and quantitative chemical lead studies and the problem of lead poisoning and buckshot injuries. *Z Chir* 1968; **93:** 216–30.

15 Bowen DI, Magauran DM. Ocular injuries caused by airgun pellets: an analysis of 105 cases. *Br Med J* 1973; **i:** 333–7.

16 Dambite GR. Svintsovnaya atrofiya zritel'nogo nerva, uspeshno lechennaya unitiolom. (Successful treatment of lead atrophy of the optic nerve with Unithiol.) *Oftalmol Zh* 1966; **21:** 329–31.

17 Sevel D, Atkins AD. Pellet gun injuries of the eye. *S Afr Med J* 1978; **54:** 566–7.

18 Laffers Z, Brehm H. Intraorbitale, extrabulbar gelegene Projektilverletzungen. *Klin Monatsbl Augenheilkd* 1980; **176:** 413–7.

19 Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1972; **14** (1): 666–7.

20 Stallard HB. In: Roper-Hall MJ, ed. *Stallard's eye surgery*. Bristol: Wright, 1980: 843.

Accepted for publication 22 December 1986.

British Journal of Ophthalmology, 1988, 72, 101–103

Ocular and cardiovascular response to topical carteolol 2% and timolol 0·5% in healthy volunteers

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SUMMARY Ocular and cardiovascular effects of carteolol 2%, timolol 0·5%, and dummy eyedrops have been measured in a single dose double-blind crossover study in six healthy volunteers. Both drugs lowered intraocular pressure and reduced exercise-induced tachycardia. Neither produced a significant change in resting heart rate or blood pressure. The two agents appear comparable as regards ocular hypotensive and cardiovascular effects.

Topical beta adrenoceptor blocking drugs (beta blockers) are now the first line of treatment in many types of glaucoma, though their use in certain individuals is restricted by adverse cardiovascular or respiratory effects resulting from systemic absorption. Timolol has been reported to cause bradycardia, syncope, arrythmias, and exacerbation of obstructive airways disease.[1] In theory beta blockers with differing properties such as cardioselectivity, partial agonist activity (intrinsic sympathomimetic activity; ISA) or reduced lipid solubility should offer advantages over timolol with respect to these adverse effects. This paper reports a comparative study of intraocular pressure (IOP) and cardiovascular effects of timolol and the newly introduced topical beta blocker, carteolol.

Material and methods

SUBJECTS

Six healthy subjects, three female and three male, aged 33 to 57 years, took part in this study. None had a previous history of cardiovascular or respiratory disease or was taking drugs of any kind. All had normal eyes, IOPs, blood pressure, peak expiratory flow, electrocardiogram, blood count, and electrolytes. The subjects were phenotyped for debrisoquine hydroxylation,[2] and all were extensive metabolisers (range of metabolic ratios 0·2 to 1·7). Non-metabolisers of debrisoquine were excluded because they may be prone to prolonged effects from small systemic doses of certain beta blockers.

Each gave written consent to participate and the study was approved by the Ethical Committee of West Lambeth Health Authority.

TREATMENTS AND STUDY DESIGN

Subjects attended on three occasions at the same time of day separated by at least seven days. On each occasion one of three treatments, carteolol 2%, timolol 0·5%, or a matching dummy solution, was administered double blind as eyedrops in a complete balanced crossover design. Two drops of drug solution (volume 0·027 ml each) were applied one minute apart to one eye, the same eye being used in each volunteer for all treatments.

MEASUREMENTS

Before and 2 and 4 hours after treatments the following measurements were made in the order given. The IOP was measured by applanation tonometry under proxymetacaine 0·5% local anaesthesia. Three readings were recorded from each eye on each occasion, the tonometer dial being read by an independent observer. Following a 10-minute supine rest period, the heart rate (HR) was recorded from an electrocardiography (ECG) and blood pressure (BP) measured by sphygmomanometry. The BP was recorded as mean BP (diastolic plus one-third pulse pressure). The HR was then measured during the last 15 seconds of an exercise period on a bicycle ergometer. The exercise level and duration had been set by a preliminary study to give an increase of heart

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rate of 80–100 beats per minute, a tachycardia of over 140 beats per minute in all subjects.

STATISTICAL ANALYSIS

Repeatability of the baseline measurements was derived from within-subject variation by analysis of variance, by means of standard methods, and expressed as a coefficient of variation (%). The findings were:

Between occasions:	IOP	11·6%
	resting HR	6·9%
	exercise HR	3·7%
	resting BP	3·8%
Within occasions:	IOP	6·7%

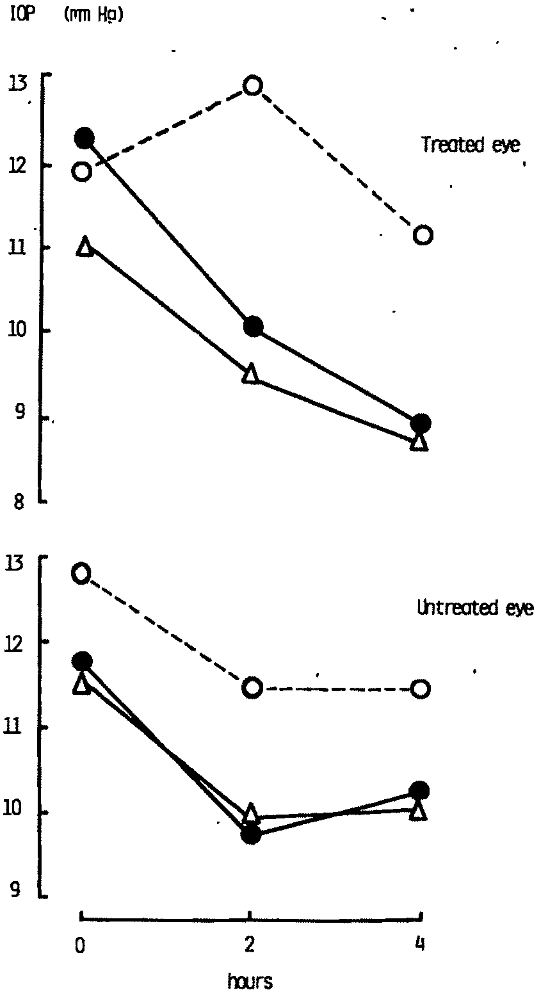

Fig. 1 *Intraocular pressure (mmHg) in treated and untreated eyes before and after instillation of carteolol 2% (●——●), timolol 0·5% (△——△), and dummy (○-------○) eyedrops.*

Differences in IOP, resting and exercise HR, and BP were analysed by paired *t* tests.

Results

INTRAOCULAR PRESSURE

IOP values for treated and untreated eyes are shown in Fig. 1. By comparison with the dummy treatment both beta blockers produced significant falls in IOP at 2 hours ($p<0·05$) and 4 hours ($p<0·05$) after instillation. In each case maximum responses were reached at 4 hours, the pressure falls being carteolol 2·2±0·6 mmHg and timolol 2·3±0·7 mmHg (mean±SEM).

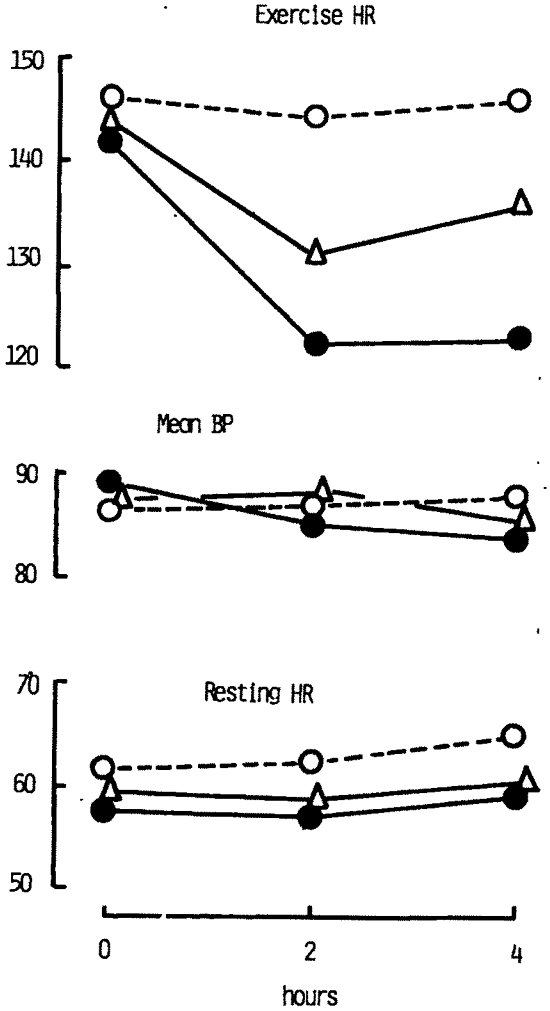

Fig. 2 *Exercise heart rate (beats per min), mean blood pressure (mmHg), and resting heart rate (beats per min) before and after instillation of carteolol 2% (●——●), timolol 0·5% (△——△), and dummy (○-------○) eyedrops.*

There was no significant difference between the two drug effects.

The IOP responses of the untreated eyes were largely obscured by differences in starting pressure. Despite this, however, carteolol produced a significant fall at 4 hours (1·2±0·3 mmHg, $p<0·05$).

CARDIOVASCULAR SYSTEM

The cardiovascular changes observed are shown in Fig. 2. Neither drug had a significant effect on resting HR or BP.

Both carteolol and timolol reduced exercise heart rate. The drug effects were greatest at 2 hours after instillation, amounting to: carteolol 22±4 beats per min ($p<0·01$), timolol 12±3 beats per min ($p<0·01$) (mean±SEM). At 4 hours the effect of carteolol was somewhat greater than that of timolol ($p<0·05$). Impaired exercise responses were associated with calf pain in some subjects.

Discussion

A number of beta blocking agents have recently become available for topical use in glaucoma. Their introduction raises two questions: firstly, will the new agents reduce IOP as well as or better than the established drug timolol; and, secondly, can this effect be achieved with equal or reduced systemic cardiovascular or respiratory side effects?

With regard to the first question it appears in this study of healthy volunteers that IOP reduction with carteolol 2% is not significantly different from that with timolol 0·5%. A recent similar study has shown no difference of hypotensive effect of metipranolol, another recently introduced agent, and timolol in glaucoma patients.[3] Betaxolol may produce less IOP reduction than timolol in glaucomatous eyes.[4]

The incidence of systemic complications of topical beta blockers is theoretically influenced by pharmacological properties of the different drugs. It has been suggested that the property of ISA, possessed by carteolol, may prevent reduction of resting heart rate which occurs when this property is absent. We did not identify a significant difference between carteolol and timolol in this respect.

For the strengths of carteolol and timolol drops used in this study it appears that carteolol reduces exercise induced tachycardia to an equal or greater extent than timolol. Our observations suggest that carteolol does not have any significant advantage or disadvantage as a topically applied beta blocker over timolol as far as IOP and cardiovascular effects are concerned.

Betaxolol is a cardioselective beta blocker, which should make it safer than non-selective agents in patients with lung disease. Van Buskirk *et al.*[5] reported its use in asthmatic patients without deterioration of pulmonary function. However, exacerbation of obstructive airways disease can occur with betaxolol,[6] indicating that its cardioselectivity is not absolute.

These examples of variation between theoretical and actual effects of topical beta blockers suggest that a period of evaluation is required before their place in treatment can be established.

We thank Dr J Gregory, of Dispersa Ltd, for a gift of carteolol eye drops and for financial support. DJB is supported by the Iris Fund for Prevention of Blindness and the Special Trustees of St Thomas's Hospital.

References

1 Van Buskirk EM. Adverse reactions from timolol administration. *Ophthalmology* 1980; **87**: 447–50.

2 Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. *Lancet* 1977; ii: 584–6.

3 Mills KB, Wright G. A blind randomised cross-over trial comparing metipranolol 0·3% with timolol 0·25% in open-angle glaucoma: a pilot study. *Br J Ophthalmol* 1986; **70**: 39–42.

4 Allen RC, Hertzmark E, Walker AM, Epstein DL. A double-masked comparison of betaxolol vs timolol in the treatment of open-angle glaucoma. *Am J Ophthalmol* 1986; **101**: 535–41.

5 Van Buskirk EM, Weinreb RN, Berry DP, Lustgarten JS, Podos SM, Drake MM. Betaxolol in patients with glaucoma and asthma. *Am J Ophthalmol* 1986; **101**: 531–4.

6 Harris LS, Greenstein SH, Bloom AF. Respiratory difficulties with betaxolol. *Am J Ophthalmol* 1986; **102**: 274–5.

Accepted for publication 22 December 1986.

British Journal of Ophthalmology, 1988, 72, 104–109

Histological appearances of the levator palpebrae superioris muscle in the Marcus Gunn phenomenon

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SUMMARY The levator palpebrae superioris muscles from 12 cases of Marcus Gunn phenomenon were examined histologically by means of histochemistry and morphometry. The appearances were of a neurogenic atrophy with pathological changes occurring in both the affected side and the clinically normal side, suggesting that the causative lesion was located in the central nervous system.

In 1883 Marcus Gunn described a case of unilateral congenital ptosis affecting the left side.[1] The salient features of the original case were contraction of the levator palpebrae muscle in association with the external pterygoid muscle, a diminished action of the levator muscle (tonic and active) in its association with other muscles supplied by the third nerve, an imperfect relaxation of the levator muscle when the eyelids were gently closed, and a diminished size of pupil on the affected side. The pupillary movements were described as being normal with no evidence of a Horner's syndrome.

The committee[1] that reviewed the findings of Marcus Gunn's case postulated the existence of abnormal connections between the third and fifth cranial nerve motor nuclei. An electromyographic study[2] of one elderly male suffering from the Marcus Gunn phenomenon (MGP) suggested that the dysfunction was located in the mid brain and brain stem. It has been suggested[3] that the ptosis and abnormal movements in the MGP are analogous to the movements seen in fish—namely, the co-ordinated jaw and spiracle musculature. An alternative explanation[4] is that the Marcus Gunn phenomenon may represent a supranuclear failure to suppress a primitive reflex.

Several studies of the morphology in congenital ptosis from 1890 to 1955 were reviewed by Berke and Wadsworth.[5] A range of gross and histological abnormalities of the levator muscle, often in association with abnormalities of the superior rectus muscle, were noted. A study of a case of left sided ptosis by Siemerling[6] showed degeneration of the levator muscle, the third cranial nerve, and nuclei on the affected side. Berke and Wadsworth[5] studied specimens from the levator muscles of patients undergoing surgery for the correction of ptosis. They found that in congenital ptosis the number of striated muscle fibres in their specimens was inversely related to the severity of the ptosis and extent of eyelid movement (levator function). In patients with Marcus Gunn phenomenon Müller's muscle and striated levator muscle fibres were present, but no comment was made on the quality of the levator muscle in these cases.

We describe the histopathological appearances of levator muscles removed from 12 patients undergoing surgery (bilateral brow suspension) to correct a ptosis due to the Marcus Gunn phenomenon.

Materials and methods

In 12 patients with ptosis and the Marcus Gunn phenomenon the levator muscles on both sides were isolated via a posterior approach. Each muscle was transected above the origin of Müller's muscle and a segment of the whole striated muscle varying in length from 3 to 10 mm was excised and placed in separate bottles containing potassium citrate and magnesium sulphate buffered ammonium sulphate fixative.[7] The eyelids were then suspended from the frontalis muscle with strips of autogenous fascia lata to correct the ptosis (bilateral brow suspension).

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The biopsy specimens thus obtained were rehydrated in the potassium citrate and magnesium buffer without ammonium sulphate, then snap frozen in nitrogen cooled isopentane. Cryostat sections were prepared and stained by the following methods: (1) haematoxylin and eosin; (2) Gomori trichrome (one step) method;[8] (3) ATP (myosin adenosine triphosphatase) at pH 4·3, 4·6, and 10·4;[9,10] (4) NADHTR (nicotinic adenine dinucleotide (reduced) tetrazolium reductase);[11] (5) non-specific acid phosphatase;[12] (6) acetylcholinesterase.[13]

The histological sections were examined by light microscopy. The diameter of individual muscle fibres and the numbers of muscle fibres were measured with eyepiece graticules. The fibre diameters of 150–200 of each of the two main muscle fibre types (type 1 or slow fibre and type 2 or fast fibre) were measured. Mean values with standard deviations for both fibre

Table 1 *Clinical data*

Case	*Sex*	*Affected side*	*Age at operation*
1	F	Right	4½ years
2	F	Left	4 years
3	M	Right	6½ years
4	M	Right	7 years
5	M	Right	17 years
6	F	Left	8½ years
7	M	Left	4¾ years
8	M	Left	7½ years
9	M	Right	7¾ years
10	F	Left	5 years
11	M	Left	5 years
12	F	Right	7¾ years
			Age at necropsy
Control I (cystic fibrosis)	M	—	15 years
Control II (road traffic accident)	F	—	10 years

Table 2 *Muscle Fibre Density (fibres/sq mm)*

Case	*Affected side*	*Clinically normal side*
1	182	192
2	356	1671
3	467	525
4	478	537
5	131	202
6	242	352
7	788	892
8	425	776
9	154	278
10	578	1638
11	183	462
12	252	285
	Right side	*Left side*
Control I	1200	1265
Control II	1541	1626

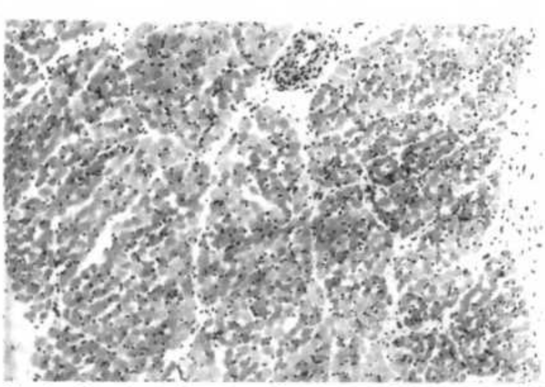

Fig. 1 *Histological section of levator muscle from a normal control subject showing a normal density of uniformly sized muscle fibres arranged in fascicles. H and E.*

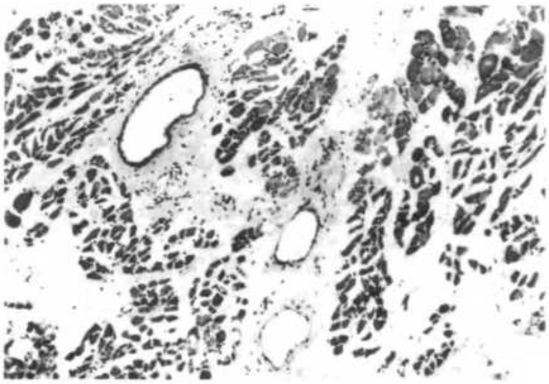

Fig. 2 *Histological section of levator muscle from an affected side (MGP) showing a marked decrease in the muscle fibre density and variation in the size of the remaining muscle fibres. H and E.*

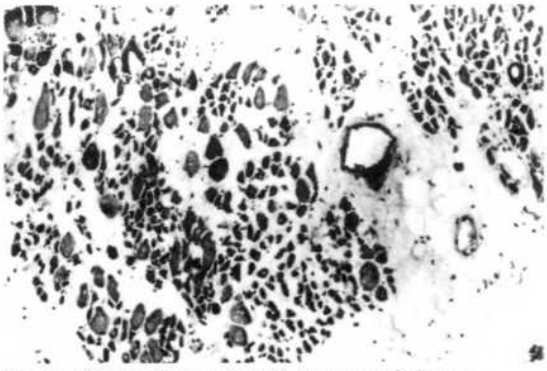

Fig. 3 *Histological section of levator muscle from a clinically normal side (MGP) showing a decrease in fibre density and variation in the size of the remaining muscle fibres. H and E.*

types and an overall value for the biopsy were calculated.

Levator palpebrae superioris muscles were obtained from two necropsy cases to act as 'normal' controls. The necropsy subjects were aged 15 years and 10 years respectively and died of cystic fibrosis and as a result of a road traffic accident. Neither case had any history of oculomotor problems or ophthalmic disease. Specimens obtained from these two cases were processed as above.

Results

The mean age at surgery was 7 years (Table 1). Of the 12 cases in the series seven (58%) were male and five (42%) female. Both sides were affected equally.

All biopsies contained striated muscle fibres. The density of the muscle fibres in the levator muscles of the control subjects was roughly equal on both sides (Table 2). The density of muscle fibres was reduced on the affected side in all cases of MGP when compared with the biopsy from the clinically normal side. In some the density was only marginally reduced from that of the clinically normal side. There was an impression that the density of muscle fibres from both sides of the patients suffering the MGP was reduced in comparison with the normal control subjects (Figs. 1, 2, 3).

In the normal control subjects the mean diameters (Table 3) for type 1, type 2, and overall muscle fibres were in the region of 18–19·5 µm, and the values for the standard deviation were approximately 3·75. Comparison of the pairs of muscles obtained from each normal control subject showed a slight variation in the values.

A wide range of values was obtained for the type 1, type 2, and overall mean fibre diameters in the various biopsies from the clinically normal sides. Comparison of the clinically normal biopsies with the paired biopsy from the affected contralateral levator muscle showed that there was a general tendency to hypertrophy of the remaining muscle fibres on the affected side (type 2 fibres more so than type 1 fibres), though some pairs of biopsies showed little difference in the values for the mean fibre diameters. Comparison of the standard deviations and histograms (Figs. 4, 5) of the two sides showed a generally wide range of values for the fibre diameters of the muscle fibres from the affected side.

Comparison of the values and histograms obtained from the normal control subjects with the clinically normal levator muscles from the affected subjects showed that there was a greater variation in the muscle fibre diameters of some of the clinically normal levator muscles (range of means 11·75–37·5 µm) than seen in the normal control levator muscles (range of means 18–19·76 µm). It would also appear that there was a tendency to overall atrophy in both affected and clinically normal sides in comparison with the clinically normal control subjects.

The distribution of type 1 and type 2 fibres in the normal control muscle gave rise to a speckled pattern (Fig. 6). The ratio of the numbers of type 1 and type 2 fibres was approximately 1:5 in all four control levator muscles and in most areas of the muscles from the patients suffering from the Marcus Gunn phenomenon. However, there was muscle fibre type grouping (with associated hypertrophy or atrophy of the grouped fibres) in many of the specimens (Fig. 7) from the affected sides in cases of Marcus Gunn

Table 3 *Muscle fibre diameters (µm)*

Case	*Age*	*Affected side*			*Clinically normal side*		
		Type 1	*Type 2*	*Overall*	*Type 1*	*Type 2*	*Overall*
1	4½	Not done	Not done	21 (8·75)	Not done	Not done	17 (5·75)
2	4	Not done	Not done	16 (8·5)	Not done	Not done	19 (9·25)
3	6½	17·5 (7)	21 (7·5)	19·75 (10)	12·25 (6·0)	15·5 (7·5)	14 (7)
4	7	15 (6)	20·75 (7·5)	17·25 (7·25)	16 (6·0)	20 (8)	18·5 (7·5)
5	17	23·75 (14·5)	40·75 (10·25)	32·0 (15·25)	31·50 (8·75)	40 (10·75)	37·5 (11)
6	8½	19 (6·75)	22·5 (10·5)	20·75 (9·0)	15·75 (4·75)	19·75 (2·4)	17·5 (5·75)
7	4¾	12 (5·5)	14·75 (6·5)	13·75 (6·25)	10·5 (3·25)	13·5 (4·25)	12·0 (4)
8	7½	15·75 (5·75)	20·75 (7·25)	18·25 (7·0)	13·25 (5·25)	16·9 (6·25)	14·75 (6·0)
9	7¾	Not done	Not done	17·75 (7·75)	Not done	Not done	22.50 (11·5)
10	5	11·5 (7·5)	12·25 (5·0)	11·75 (6·75)	12·75 (5·5)	11·25 (4·25)	11·75 (4·75)
11	5	17·25 (4·75)	21 (7·0)	19·5 (6·25)	13·5 (4·25)	13·25 (5·5)	13·25 (5·0)
12	7¾	13·5 (4·5)	19·25 (8·5)	16·75 (9)	12·25 (5·25)	16·5 (7·5)	14·75 (7·0)
		Right side			*Left side*		
Control I	15 yr	19 (3·75)	19·75 (3·75)	19·5 (3·75)	18·75 (3·25)	19·0 (4·25)	19·0 (3·75)
Control II	10 yr	18·5 (3·75)	19·25 (3·75)	18·75 (3·75)	17·75 (4·5)	18·5 (4·75)	18·0 (4·75)

SD shown in parentheses.

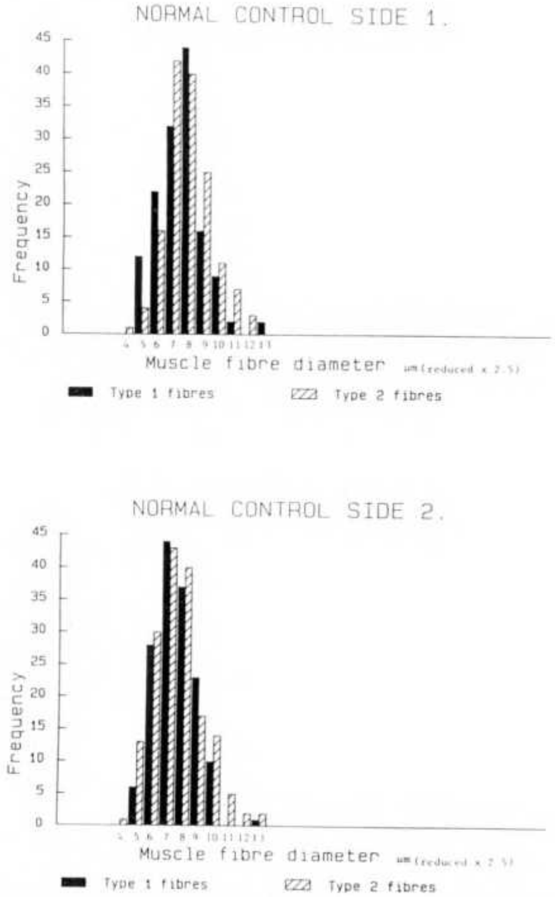

Fig. 4 *Histograms showing the distribution of type 1 and type 2 muscle fibre diameters in levator muscles from a normal control subject.*

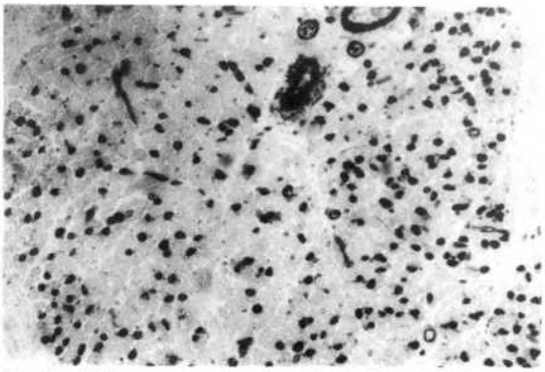

Fig. 6 *ATPase preincubated at pH 4·3. Histological section of levator muscle from a normal control subject showing the same area as Fig. 1. Type 1 fibres are black and type 2 are pale grey. Note the speckled pattern.*

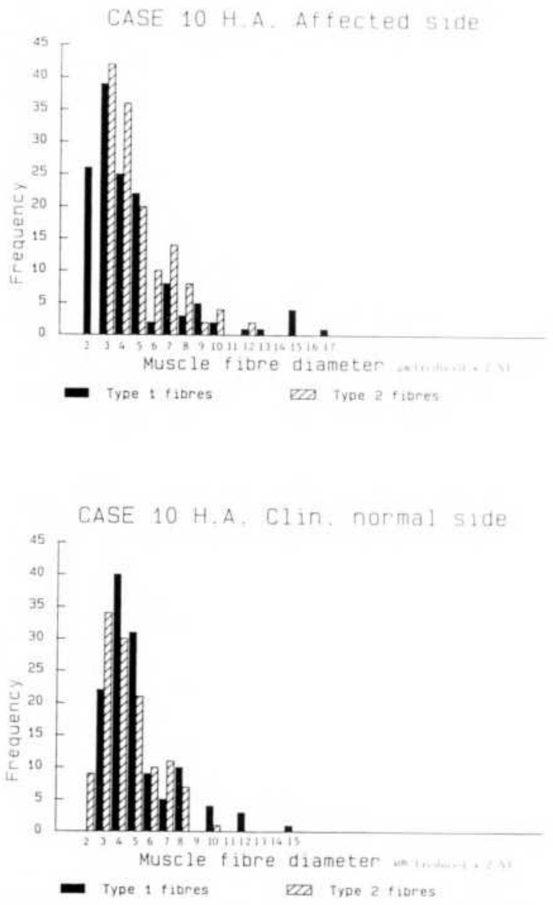

Fig. 5 *Histograms showing the distribution of type 1 and type 2 muscle fibre diameters in a subject affected by the Marcus Gunn phenomenon. Note the widening of the distribution of fibre diameters and the overall shift to the left indicating generalised atrophy, more obvious on the affected side but present also on the clinically normal side.*

phenomenon. In some of the specimens from the clinically normal side there were some small areas of fibre type grouping.

Histological sections from both sides of patients affected by MGP showed central accumulation of mitochondria within individual muscle fibres (Fig. 8). This change from the normal granular pattern of mitochondria seen in fibres from the normal control levator muscles (Fig. 9) was seen in small groups of muscle fibres scattered throughout the biopsies from both the affected and clinically normal sides.

Acid phosphatase staining showed no evidence of any lysosomal accumulations within muscle fibres or the presence of macrophages in the perimysium. No evidence of any synapses was seen in any of the biopsies with acetylcholinesterase.

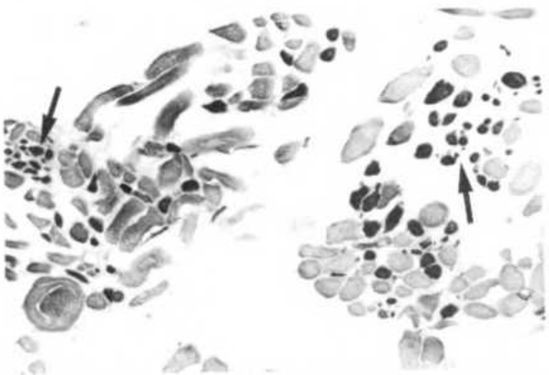

Fig. 7 *ATPase preincubated at pH 4·3. Histological section of levator muscle from an affected side (MGP) showing a loss of the normal speckled pattern, with grouping (arrowed) of the type 1 muscle fibres (stained black) and the wide variation in the muscle fibre diameter.*

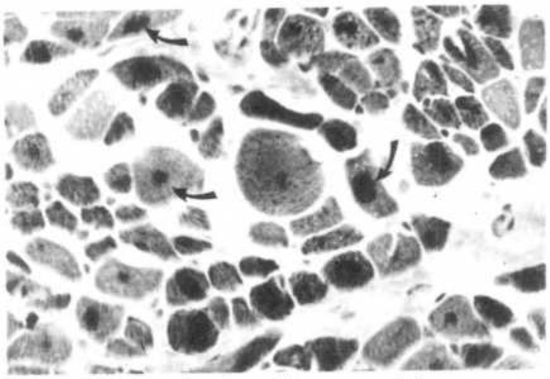

Fig. 8 *Histological section of levator muscle from an affected side (MGP) showing clumping of the mitochondria in the centre of muscle fibres (arrowed). Note the wide variation in muscle fibre diameter. Gomori trichrome stain.*

Discussion

The site of our muscle biopsies from the distal end of the levator muscle close to the origin of the aponeurosis and the use of a fixative solution in processing combined to make them difficult to interpret. However, it has been possible to identify trends in the appearances and, indeed, definite lesions in the 24 biopsies, especially when they were compared with similar material obtained from two cadavers. Using an ammonium sulphate fixative required that the specimens were rehydrated prior to freezing. This needed careful attention so as to minimise distortion of the morphology of the small biopsy specimens. The use of a fixative was justified by the need to transport the specimens from one hospital to another and because it allowed a greater degree of freedom for the surgeon and laboratory.

The findings suggest that there is a loss of muscle fibres in the affected levator muscle relative to the clinically normal side. Furthermore, there is an impression that the levator muscles on both the affected and ostensibly normal sides in patients suffering the Marcus Gunn phenomenon contain fewer fibres than the equivalent area in the normal control levator muscles.

Morphometry of the muscle fibres suggests that there is both atrophy and compensatory hypertrophy of the remaining muscle fibres in the affected levator muscle in comparison with the clinically normal levator muscle and the normal control levator muscle. The presence of small fibres suggests that the atrophic process may be ongoing, but the relative absence of pyknotic muscle fibres and macrophages in the perimysium further suggests that the process may be in abeyance in some cases at the time of surgery. The impression from the morphology is of a weak muscle in a compensating or steady state.

The presence of muscle fibre type grouping with associated loss of fibres and atrophy and hypertrophy of the remaining muscle fibres suggests that the underlying process is a neurogenic atrophy. There appears to have been a partial loss of the nerve supply to areas of the muscle with reinnervation, resulting in a loss of the normal speckled pattern of type 1 and type 2 fibres. The underlying principle is that if, for example, in an area in which type 2 muscle fibres lose their nerve supply and are reinnervated by an adjacent sprouting nerve that has a type 1 pattern of electrical stimulation, then the previous type 2 muscle fibres undergo physiological and biochemical adaptation to become type 1 fibres as recognised by

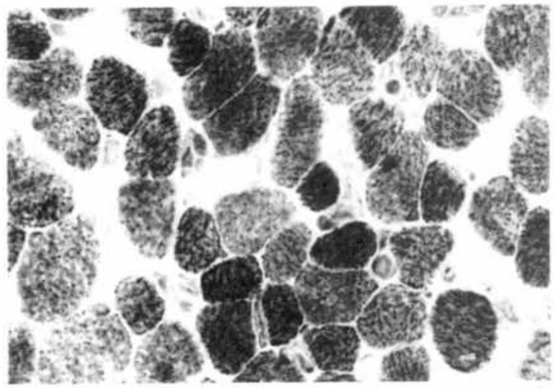

Fig. 9 *Histological section of levator muscle from a normal control subject showing the normal granular distribution of mitochondria within the muscle fibres and the greater uniformity of muscle fibre diameter. Gomori trichrome stain.*

their histochemical staining reaction. This may result in focal areas assuming a monomorphic (rather than the normal speckled) type of fibre distribution dictated by the available nerve supply.

Examination of the clinically normal levator muscle in 10 of the 12 cases showed that they too contain fewer fibres than would be expected in a normal muscle in comparison with the normal control levator muscles. Two cases showed values consistent with normal fibre densities. Similarly, morphometry of the clinically normal levator muscle showed that there was a spread of muscle fibre diameters that was greater than that seen in the normal control levator muscles owing to the presence of both atrophic and hypertrophic forms. Fibre type grouping was present in some of the clinically normal muscles, though less obviously than seen in muscle from the affected side.

Both sides in the patients affected by the Marcus Gunn phenomenon showed central accumulations of mitochondria within scattered groups of individual fibres. This is not an appearance generally seen in normal skeletal or extrocular muscle but has been noted[14 15] in biopsies of overacting inferior oblique muscles excised during the surgical treatment of strabismus. It was construed as being a reactive change to an increased work load or stress, but the rationale behind this change is uncertain.

Our findings suggest that the process underlying the Marcus Gunn phenomenon is a neurogenic atrophy with aberrant reinnervation and that it is a bilateral process with one side being severely affected and the clinically normal side being affected to a lesser degree. This may explain case reports of bilateral Marcus Gunn phenomenon. It would also indicate that the initiating pathological process was probably located within the central nervous system, that is, brain stem, rather than being a peripheral lesion of the third cranial nerve and that the initial lesion had occurred in utero.

References

1 Gunn RM. Congenital ptosis with peculiar associated movement of the affected lid. *Trans Ophthalmol Soc UK* 1883; **3:** 283–7.

2 Hepler RS, Hoyt WF, Loeffler JD. Paradoxical synkinetic levator inhibition and excitation: an electromyographic study of unilateral oculopalpebral and bilateral mandibulo palpebral (Marcus Gunn) synkinesis in a 74-year-old man. *Arch Neurol* 1968; **18:** 416–24.

3 Harman NB. The innervation of the orbicularis palepbrum muscle. *Trans Ophthalmol Soc UK* 1903; **23:** 356–72.

4 Wartenberg R. Winking-jaw phenomenon. *Arch Neurol Psychiatry* 1948; **59:** 734–53.

5 Berke RN, Wadsworth JAC. Histology of levator muscle in congenital and acquired ptosis: *Arch Ophthalmol* 1955; **53:** 413–28.

6 Siemerling E. Anatomischer Befund bei einseitiger congenitaler Ptosis. *Archiv für Psychiatrie und Nervenkrankheiten* 1891–2; **23:** 764–74.

7 Croker BP, Bosen EH, Brinn NT, Hammond FA. A fixative for use in muscle histochemistry. *J Histochem Cytochem* 1983; **31:** 110–2.

8 Engel WK, Cunningham GG. Rapid examination of muscle tissue. *Neurology* 1963; **13:** 919–23.

9 Brooke MH, Kaiser KK. Three 'myosin ATPase' systems: the nature of their pH lability and sulphydril dependence. *J Histochem Cytochem* 1970; **18:** 670–2.

10 Hoogenraad TU, Jennekens FGI, Tan KEWP. Histochemical fibre types in human extraocular muscles. An investigation of inferior oblique muscles. *Acta Neuropathol (Berl)* 1979; **45:** 73–8.

11 Pearse AGE. Histochemistry: theoretical and applied. 3rd ed. London: Churchill-Livingstone; 1972: **2:** 1342–3.

12 Buritone MS. Enzyme histochemistry and its application in the study of neoplasms. New York: Academic Press. 1962: 276.

13 Bancroft JD. *Histochemical technique*. London: Butterworths, 1967: 211–3.

14 Spenser RF, McNeer KW. Structural alterations in overacting inferior oblique muscles. *Arch Ophthalmol* 1980; **98:** 128–31.

15 Mayer E, Ludatscher RM, Zonis S. Primary and secondary overacting inferior oblique muscles: an ultrastructural study. *Br J Ophthalmol* 1984; **68:** 416–20.

Accepted for publication 15 December 1986.

British Journal of Ophthalmology, 1988, **72**, 110–115

Why should surgery for early-onset strabismus be postponed?

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SUMMARY The author presents a continued study of 82 cases of pseudoparalysis of the bilateral rectus muscles in early-onset convergent strabismus following early surgery. Up to 10 years after surgery motor results show that 72% of cases remain within ±10 prism dioptres after a single surgical procedure. Sensorial findings corroborate the results of other authors' studies in that binocular association is only achieved in those patients where surgery was carried out at a very young age, not older than 1 year. Surgical procedures consisting of bimedial rectus recession with retroequatorial myopexy are described and the development of alphabetical syndromes and dissociated vertical divergence discussed. The evolution of refraction in these cases is also shown.

Early treatment of strabismic amblyopia is no longer contested. Paradoxically, early strabismus surgery still meets with some controversy. Visual acuity and binocular functions do not evolve as a pair. Their development depends on there being no disturbance in the interaction between a maturation process which follows a genetic programme and visual experience which represents indispensable epigenetic influences.

Studies of the age at which adult-level visual acuity is achieved in normal infants give different results according to the testing techniques used. Results range from 4 to 6 months[1] and 4 years.[2] Stereoacuity, however, is widely found to mature at an early age, from 3 to 6 months.[2] Recent studies by Held *et al.*[3] have shown that 'In comparison with the relatively slow development of visual acuity, the time course for the development of stereoacuity is extremely rapid.' This corroborates the conclusions of the neurophysiologist Vital-Durand[4] whereby 'acuity follows rather than precedes the development of binocularity.' These findings correspond with my own clinical experience.

Material and methods

The first 82 cases of early-onset strabismus operated upon between the ages of 6 and 30 months have already been the subject of a previous publication.[5] All 82 cases conform to the definition of pseudoparalysis of the lateral recti. Surgery is always sym-

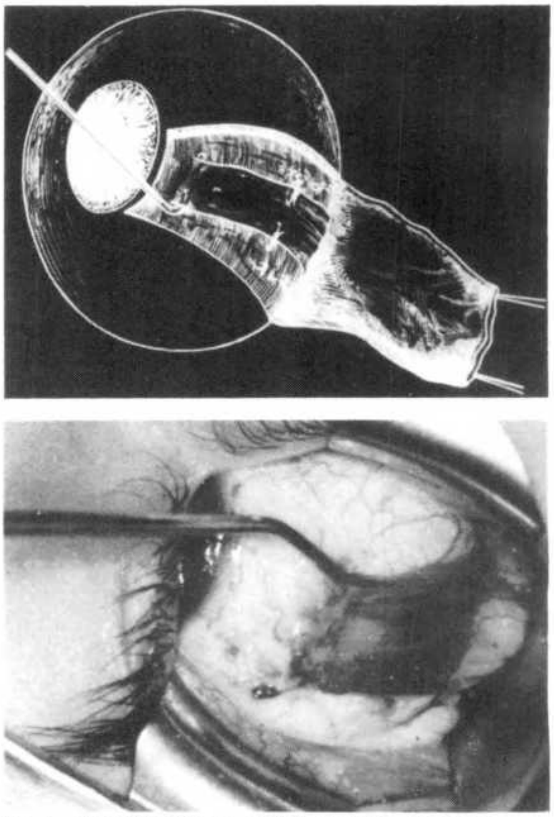

Fig. 1 Top: *The retroequatorial myopexy—schematic diagram.* Bottom: *The retroequatorial myopexy—clinical appearance.*

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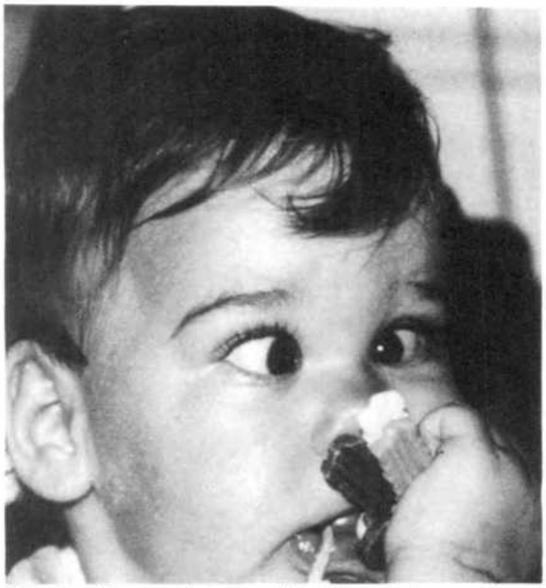

Fig. 2A *Preoperative crossed fixation with abnormal head posture. Age 8 months.*

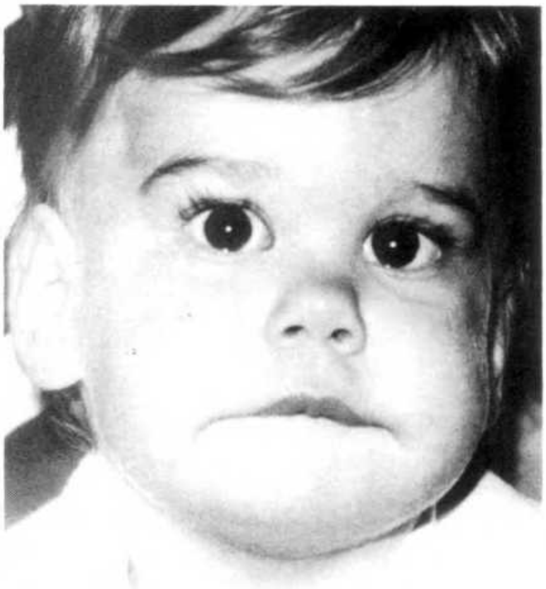

Fig. 2B *Age 10 months—one week after surgery.*

metrical on the two medial recti, consisting of muscle recession with a retroequatorial myopexy.[6] This operation is also known as 'Cüppers' faden operation' or 'posterior fixation suture', but I prefer the term, 'more precise though considered by some as too ponderous, retroequatorial myopexy' (von Noorden).[7]

Retroequatorial myopexy was introduced by Cüppers in Germany in 1974. The principle of this procedure is muscle anchorage to the sclera *behind* the equator (Fig. 1). This reduces the effective arc of contact between the muscle and the globe, thus selectively weakening the muscle in its field of action. There is no effect on the primary position or away from the muscle's field of action. The result of this surgery is reduction of the motor response, while the associated muscle recession corrects the eye position. The variability of the angle of deviation in this form of strabismus is well known. Surgery consisting of combined recession and retroequatorial myopexy permits a more appropriate correction than conventional surgical techniques. Far fewer immediate or late-occurring consecutive divergent deviations are observed, because the necessary muscle recession, when associated with the myopexy, is much smaller.

The myopexy is placed at 13 mm from the original muscle insertion. Exceptionally it may be placed at 12 mm in very small eyes. The associated muscle recession is 2 mm for deviations up to 25°, 3 mm for those exceeding 25°.

Results

The first study of these 82 cases gave[5] the following results: excellent results concerning the angle of strabismus, with suppression of crossed fixation and the usual abnormal head posture, results showing notable stability with time (Figs. 2 and 3); immediate and complete recovery of abduction, satisfactory conjugate ocular movements, and good vergence; unblocking of amblyopia in a few cases refractory to preoperative treatment.

I have continued to follow up these 82 cases personally with the same two orthoptists. With the statistics brought up to date, there is a current minimum follow-up of at least one year where further surgery was necessary, and a maximum of 10 years. 80% of cases fall into the group of five years' minimum follow-up.

MOTOR RESULTS

Horizontal angle of strabismus

The latest postoperative angle of strabismus and the number of muscle procedures carried out are given in Table 1. This shows that 72% of cases had a long-term angle of not more than ±10 prism dioptres (PD) after one single horizontal muscle surgical procedure.

Alphabetical syndromes and vertical (oblique) muscle surgery. Fourteen cases required further surgery because of alphabetical syndromes (9V, 4A, 1X). The relative failure of single-step surgery was

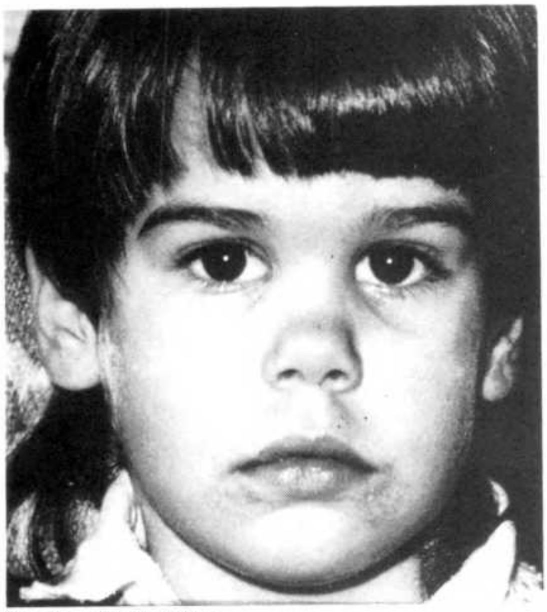

Fig. 2C *Age 3½ years.*

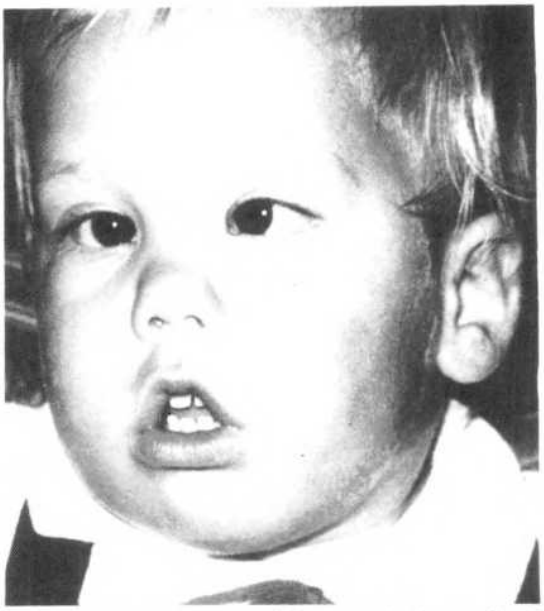

Fig. 3A *Preoperative crossed fixation with abnormal head posture. Age 15 months.*

thus mainly due to oblique muscle factors. Difficulty in diagnosing alphabetical syndromes in young infants is one argument used by those surgeons opposed to early surgery. In this first series of 82 cases purely horizontal muscle surgery was carried out in those infants under 20 months of age. Alphabetical syndromes in this group (11 cases out of 36) systematically underwent further surgery. In infants aged 21 to 30 months combined horizontal-vertical muscle surgery was carried out in seven cases, and only three required separate oblique muscle surgery. However, in a subsequent series of 70 cases with the same proportion of alphabetical syndromes combined horizontal-vertical muscle surgery was carried out in

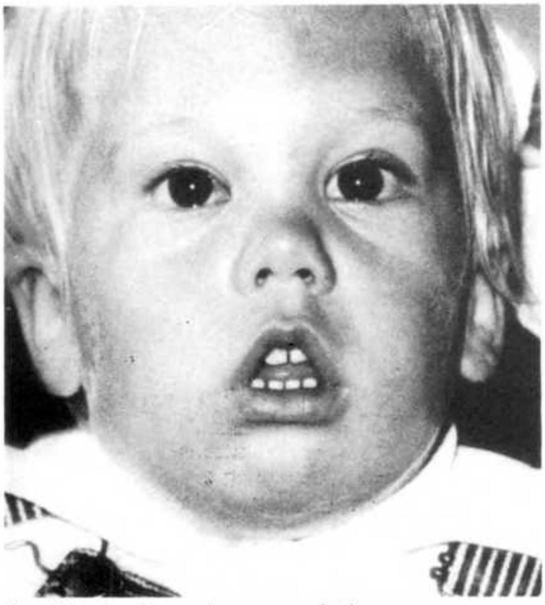

Fig. 3B *Age 16 months—one week after surgery.*

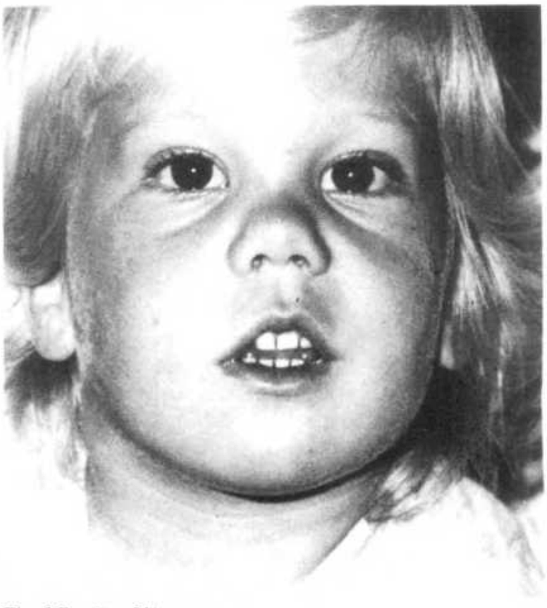

Fig. 3C *Age 2¼ years.*

Table 1 *Long-term residual angle*

Angle PD	*Horizontal procedure*		*Horizontal procedures*	
	No. cases	*%*	*No. cases*	*%*
Up to ±4	35	43 } (72)	4	5
>4 to ±10	24	29	0	
>10	18	22	1	1

a larger number of cases owing to more thorough examination even in the youngest age group, thus reducing the number of reoperations.

Alphabetical syndromes and age. 20% of cases presented an alphabetical syndrome before the age of 20 months, 36% between 20 and 30 months, according to our series of patients. Quéré, *et al.*[8] noted them in 64% of cases and favoured postponement of surgery until 2½ to 3 years of age. Bérard[9] observed these syndromes in almost all cases, and considered 3 years as being the ideal age for surgery. It would thus appear that the vertical syndrome is secondary to a neglected horizontal deviation.

Dissociated vertical divergence (DVD). DVD was almost the rule (77% of cases), appearing at the earliest at 1 year, at the latest at 7 years, but in two-thirds of cases between 2 and 4 years of age. As can be seen in Fig. 4, age at the time of surgery had no influence on the development of DVD. Cosmetically unsatisfactory decompensation of DVD requiring specific complementary surgery was necessary in only two cases, that is, 3% of the total number.

REFRACTIONAL RESULTS

The evolution of refractive error up to the age of 10 years in these 82 cases is shown in Fig. 5. Changes in refractive error followed essentially the same course as that described by Slapater[10] and Brown,[11] where hypermetropia was shown to increase up to the age of 8 years, in contrast to Chavasse's findings.[12] Thus early surgery consisting of bimedial recession with retroequatorial myopexy did not influence the evolution of refractive error.

SENSORIAL RESULTS

Our series of 82 cases is divided for closer study into six-monthly groups according to the patient's age at the time of surgery. The following criteria are required for positive binocular responses: 'coarse' stereopsis, moderate convergent and divergent fusion range, four dots on the Worth test, and crossed Bagolini striated glasses. The results are as given in Fig. 6. There is no question of real binocular single vision, even in cases of orthotropia. However, these figures show that the quality and frequency of binocular association diminished as the age at the time of surgery increased. The degree of residual angle (Fig. 7) was also an important factor in the acquisition of binocular association, but only on the following

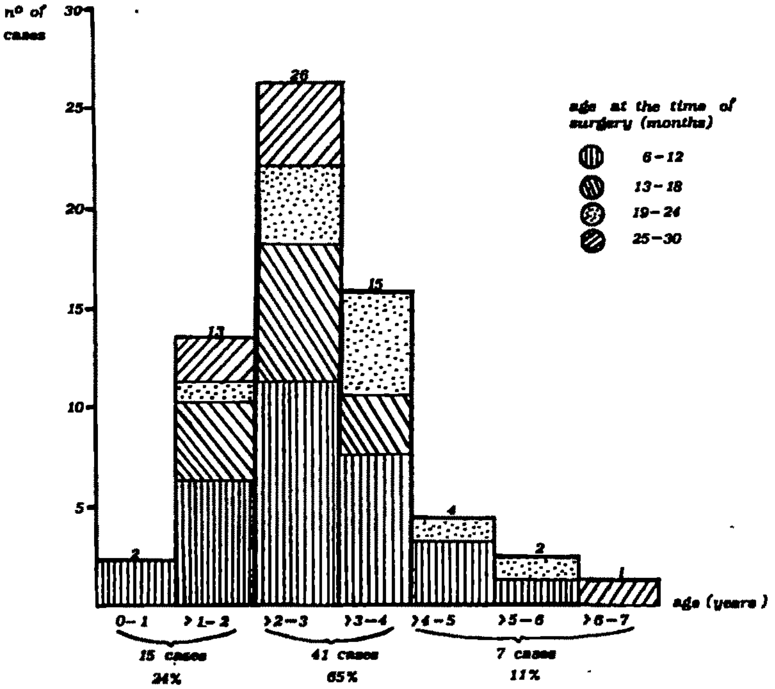

Fig. 4 *Appearance of dissociated vertical divergence.*

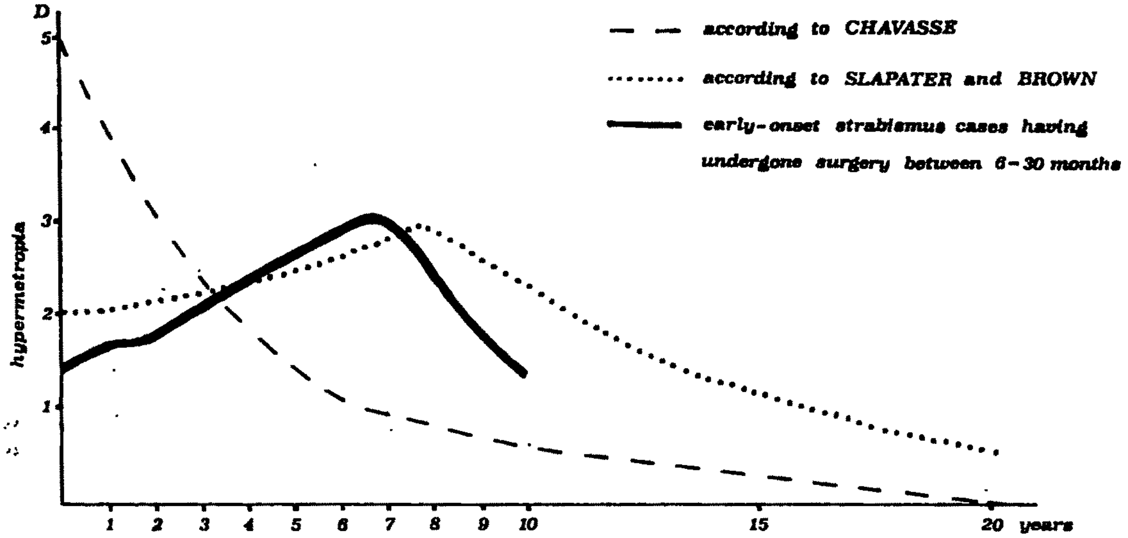

Fig. 5 *Evolution of refractive error.*

condition: the smallest residual angle is of any interest only for those patients having undergone surgery before the age of 1 year. Of the 13 cases with binocular association in the smallest angle group, 10 were operated upon between 6 and 12 months old, and one in each of the following six-month periods. Even in the larger-angle groups binocular association may be hoped for where surgery is carried out at a very young age. These results confirm studies by Archer and associates[13] in testing stereopsis, whereby 'the most striking feature was that the four patients with positive results were also the four youngest

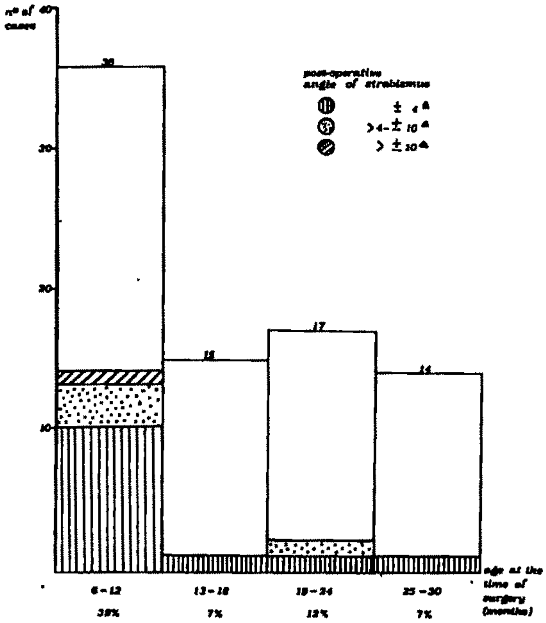

Fig. 6 *Binocular responses according to age at time of surgery.*

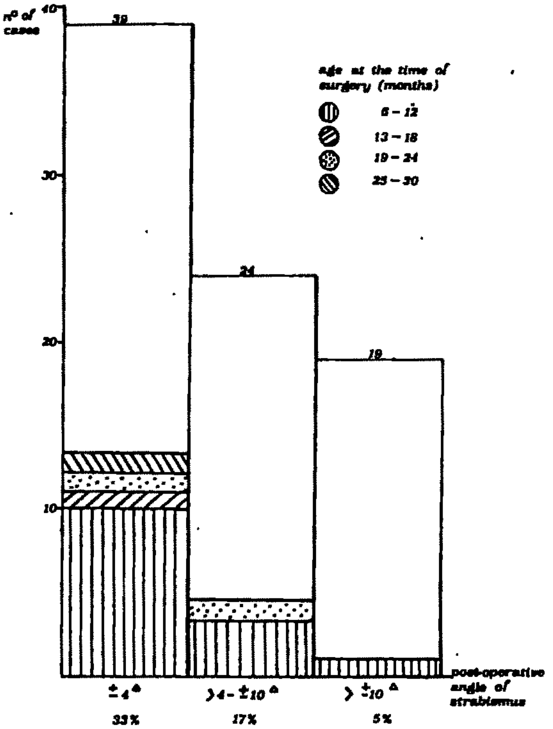

Fig. 7 *Binocular responses according to postoperative angle of strabismus.*

infants at the time of surgery (ages ranging from 6 to 8 months).'

Discussion

In view of these findings it cannot be said that the functional results of early surgery are no better than those where surgery is postponed to around 2½ to 3 years of age.[8] Our motor and sensorial results corroborate those given in studies by Mohindra *et al.*[14] and Ing,[15] where the limit of 24 months is fixed, beyond which a certain degree of stereoscopic vision may no longer be acquired if binocular coupling has had no occasion to be practised up to that time. I share Helveston's view where 'to our knowledge there is nothing to be gained from delaying surgery in a child who is considered a candidate for eventual surgical treatment.'[16] However, the latter's surgical protocol of 'en bloc' bimedial rectus recession[17] is essentially compensatory at a time when the problem is primarily dynamic, and where passive elements are negligible. Although immediate alignment with such procedures is reported to be good at 82%,[16] up to 30% of these cases require further surgery for later occurring esotropia. In our series of 82 cases of bimedial rectus recession associated with retro-equatorial myopexy, a single horizontal muscle procedure was found to be sufficient to obtain immediate and long-term alignment (to within ±10 PD) in 72% of cases, with no further surgery necessary.

In conclusion, these results are an indication not for early surgery but rather for immediate surgery, or surgery deferred only the short time necessary for preoperative treatment of any amblyopia. Indeed, why postpone surgery for early-onset strabismus?

I thank my orthoptist, Miss S E Houghton, for her help in the preparation and translation of this paper.

References

1 Marg E, Freeman DN, Peltzman P, Goldstein PJ. Visual acuity development in human infants: evoked potential measurements. *Invest Ophthalmol Vis Sci* 1976; **15**: 150–3.

2 Gwiazda JE, Birch EE, Held R. Le développement de la vision chez l'enfant. *Recherche* 1981; **12**: 1348.

3 Held R, Birch E, Gwiazda J. Stereoacuity of human infants. *Proc Natl Acad Sci USA* 1980; **77**: 5572–4.

4 Vital-Durand F. Données nouvelles sur le système visuel. 2e partie: Développement et plasticité des voies visuelles. *J Fr Ophthalmol* 1983; **6**: 319–23.

5 Deller M. Single surgical procedure in the management of pseudo-paralysis of the lateral recti. In: Boschi MC, Frosini R, eds. *Strabismus. Proceedings of the International Symposium on Strabismus*. Florence: Consilium Europaeum Strabismi Studio Deditum, 1982: 503–7.

6 Deller M. Les techniques de l'opération du fil. *J Fr Orthoptique* 1978; **10**: 89–96.

7 Von Noorden G. *Binocular vision and ocular motility*. St Louis: Mosby, 1980: 455.

8 Quéré MA, Pechereau A, Lavenant F. Etude statistique de l'angle de base et de l'intensité du spasme dans les ésotropies fonctionelles (conséquences chirurgicales). *J Fr Ophtalmol* 1985; **8**: 255–61.

9 Bérard PV. In: Bérard PV, Quéré MA, Roth A, Spielman A, Woillez M, eds. *Chirurgie des strabismes*. Paris: Masson, 1984: 248.

10 Slapater FJ. Age norms of refraction and vision. *Arch Ophthalmol* 1950; **43**: 466–81.

11 Brown EVL. Net average yearly changes in refraction of atropinized eyes from birth to beyond middle life. *Arch Ophthalmol* 1938; **19**: 719.

12 Chavasse B. In: *Worth and Chavasse's squint*. 8th ed. London: Baillière, Tindall and Cox, 1950: 23.

13 Archer SM, Helveston EM, Miller KK, Ellis FD. Stereopsis in normal infants with congenital esotropia. *Am J Ophthalmol* 1986; **101**: 591–6.

14 Mohindra I, Zwaan J, Held R, Brill S, Zwaan F. Development of acuity and stereopsis in infants with esotropia. *Opththalmology* 1985; **92**: 691–7.

15 Ing MR. Surgical alignment for congenital esotropia. *Controversies* 1984; **21**: 76–7.

16 Helveston EM. Options in the treatment of congenital infantile esotropia. *Trans Ophthalmol Soc UK* 1983; **103**: 139–42.

17 Helveston EM. *Atlas of strabismus surgery*. St Louis: Mosby, 1977: 211.

Accepted for publication 15 December 1986.

British Journal of Ophthalmology, 1988, 72, 116–126

Growth and contractility of cells from fibrocellular epiretinal membranes in primary tissue culture

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SUMMARY Cells grew out in tissue culture from 37 of 53 fibrocellular epiretinal membrane explants, those from membranes of less than four months' clinical duration growing more consistently, more rapidly, and more exuberantly than those from membranes of more than four months' clinical duration. Electron microscopy demonstrated prominent microfilaments in the cytoplasm of some of the cells, and immunostaining for actin showed great variations in the pattern and intensity of staining. An ATP contraction assay conducted on 44 detergent-extracted cells and 47 intact cells revealed in each case a 30% average reduction in cell area. Immunostaining for cytokeratins following the ATP assay showed no significant difference in cell contraction between epithelial cells and non-epithelial cells. Clinical duration of the membrane had no significant influence on the contractility of cells growing from the explant.

Contractile epiretinal membranes (ERMs) cause distortion and detachment of the retina in such diverse clinical settings as ocular trauma, ischaemia, and inflammation, but they are particularly extensive and destructive of vision when complicating the treatment of rhegmatogenous retinal detachment—so-called proliferative vitreoretinopathy (PVR). The cellular components of ERMs are also diverse even within ERMs of similar aetiology. In PVR, for example, morphological and immunohistochemical investigations of surgically excised ERMs have demonstrated macrophages, fibroblasts, glial cells, and pigment epithelial cells.[1-5] All these cell types grow out from explants of ERMs in tissue culture,[6-8] though the proportions of cells in culture presumably reflect not only the initial cell composition of the ERM but also the relative viability, proliferative capacity, and migratory activities of cells together with the effects of preferential growth (selection) within any particular tissue culture medium. A recent report from our laboratory demonstrated a significant difference in the cellular composition and collagen content of excised ERMs according to clinical ERM duration,[9] and this study seeks to determine, firstly, whether such differences are reflected in the growth characteristics of ERMs in tissue culture.

Contraction of ERMs is thought to be a cell mediated event akin to that seen in skin wounds and granulation tissue.[10 11] The scar tissue fibroblasts have been called 'myofibroblasts' because of the prominence of contractile elements within their cytoplasm. Assuming that cells responsible for ERM contraction (or their immediate progeny) are represented among those cells growing out from our ERM explants in primary tissue culture, we have also investigated their cytoplasmic contractile elements by electron microscopy and immunostaining for actin, and have monitored the contractility of individual cells in response to adenosine triphosphate (ATP). We further investigated (1) whether prior detergent treatment of cells was necessary in order to demonstrate contractility, (2) whether the clinical age of the ERM affected contractility, and (3) whether any difference in contractility could be demonstrated between epithelial cells (indicated by antiprekeratin immunostaining)[5] and other cells in the cultures, since pigment epithelial cells have been especially implicated in PVR.[2]

Materials and methods

TISSUE CULTURE

A total of 53 fibrocellular ERMs were obtained for tissue culture during closed vitrectomy procedures. The ERMs were associated with a variety of condi-

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Table 1 *Aetiology of ERMs*

	Number of ERMs	*Clinical duration*		*Outgrowth within 4 weeks*
		Early	*Late*	
PVR	34	20	14	26
Trauma	7	4	3	6
Vascular occlusion	3	0	3	1
Others	9	2	7	4
Total	53	26	27	37

PVR = proliferative vitreoretinopathy.

tions and were subgrouped into those of less than four months' clinical duration ('early' membranes) and those of four months' duration or longer ('late' membranes) (Table 1). Of the 53 ERMs 26 were the subject of an earlier preliminary communication.[7]

The segments of membrane (explants) were settled on the base of 25 cm Falcon flasks and held in place by overlying coverslips and fed with culture medium. The medium consisted of 10% fetal calf serum (Gibco), 10% newborn calf serum (Gibco) in 199 medium (Gibco). Cultures were maintained at 37°C in an atmosphere of 5% CO_2 and air with 100% humidity (Leec incubators). All cultures were examined routinely with an inverted phase microscope (Olympus) and refed once a week. If the explants did not develop a cellular outgrowth within four weeks, the culture was considered non-viable and abandoned. For all viable cultures the time taken before the first cells migrated from the explant (latent period) was recorded. Subsequent growth in primary culture was classified into three stages: stage 1 was a patchy outgrowth involving less than 50 cells; stage 2 was a more uniform cellular spread involving more than 50 cells (Fig. 1); while stage 3 was a packed culture (Fig. 2). The present study was restricted to primary cultures because it was considered that such cells might be more akin to cells 'in situ' than cells cultured through one or more passages.

TRANSMISSION ELECTRON MICROSCOPY (TEM)

If a membrane was sufficiently large, a portion was taken for TEM while the remainder served as an explant for tissue culture. In addition, some membranes with their resultant outgrowth of cells were processed from culture for TEM. All specimens were fixed with 3% glutaraldehyde in cacodylate buffer, postfixed in 1% buffered osmium tetroxide, dehydrated through graded alcohols, and embedded in Araldite. Ultrathin sections were stained with uranyl acetate and lead citrate and viewed in a JEOL 100c electron microscope.

ATP ASSAY

Ninety-one cells growing on coverslips from 13 ERMs (from two to 27 cells from each membrane) were assayed. The majority of cells to be assayed grew from ERM explants of specimens from eyes with PVR. Forty-eight cells grew from seven early ERMs and 43 cells from six late ERMs. The cells were washed in phosphate buffered saline (PBS) and then 44 cells from seven membranes (both early and late) were exposed to 0·2% Triton X-100 in stabilisation buffer for two minutes at room temperature; the other 47 cells from six ERMs were not so treated. The stabilisation buffer consisted of 0·01 M Tris-HCl (pH 7·6), 0·14 M NaCl, 0·005 M $MgCl_2$, and 4% poly-

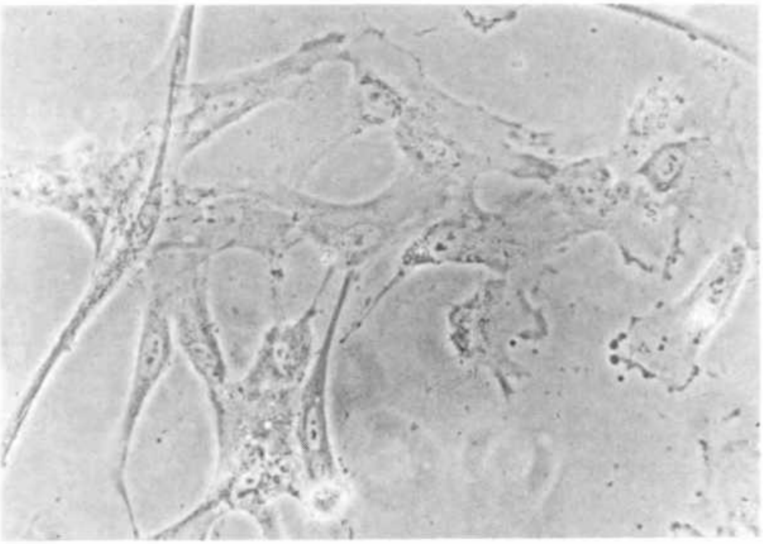


Fig. 1 *Cells growing out from an ERM explant have reached stage II. ×550.*

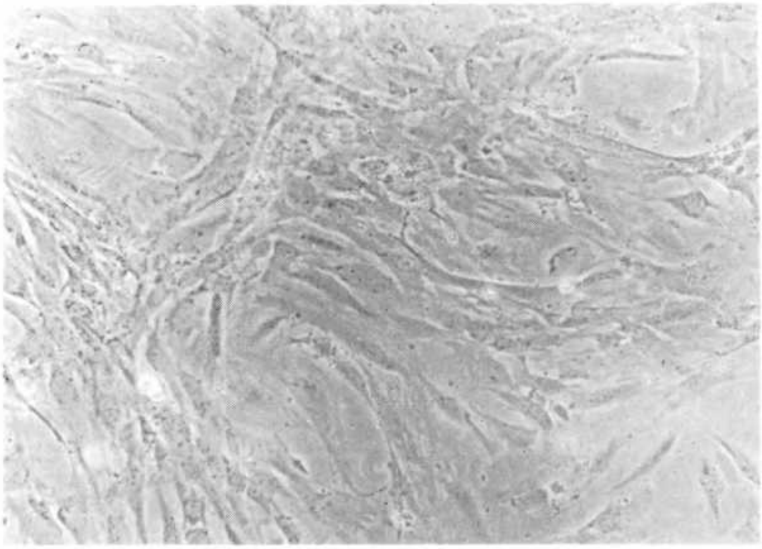


Fig. 2 *Cells from an ERM approaching confluence. ×300.*

ethylene glycol 6000. This is thought to preserve much of the intracellular contractile filament system while allowing the detergent to open up the cell for easy penetration of ATP.[12] Those cells which went through the detergent extraction process were washed in PBS.

Thereafter the detergent treated cells and untreated cells on coverslips were placed on the heated stage (37°C) of an inverted phase microscope (Olympus). Individual cells or multiple discrete cells which had clear outlines were selected, located, and centralised with a × 20 phase objective lens as soon as possible, and a photograph was taken of this field for further reference. Without altering the field the PBS was replaced with contraction buffer, to which was added ATP to a concentration of 0·1 mM. The contraction buffer consisted of 0·01 M Tris-HCl, 0·03 M KCl, 10 μm $CaCl_2$, and 0·005 M $MgCl_2$ (pH 7·0). Photographs of the selected cells were taken every minute for the first 10 minutes and thereafter a photograph was taken every 10 minutes up to one hour. Thus a total of 16 negatives were available for each cell from each experimental 'run'. The film was passed through a film reader (Zeiss) with a × 17·5 objective lens and projected on to an upright screen. The outline of each cell was drawn at various time periods during the run. The area of the cells was then measured by outlining the cell with a cursor integrated with a semiautomated image analysis system (MOP Videoplan, Kontron).

IMMUNOSTAINING

Coverslips of cultured ERM cells or of the cells after undergoing Triton X-100 treatment and/or MgATP assay were washed in PBS and air dried prior to indirect immunofluorescence staining, which was conducted according to procedures outlined in previous publications.[4,5,7] The primary antibody used for identification of epithelial cells was antiprekeratin raised in guinea-pigs (Miles Scientific) and for demonstration of actin was antiactin raised in rabbits (Dako Corporation). The second antibodies were fluorescein isothiocyanate (FITC) conjugated goat antirabbit IgG, FITC conjugated goat anti-guinea-pig IgG and tetramethylrhodamine isothiocyanate (Rh) conjugated goat antirabbit IgG. For such single labelling investigations FITC antispecies IgG was used to demonstrate the primary antibody. In addition, double labelling studies were conducted on non-assayed cells in which cytoplasmic actin was indicated by indirect labelling with Rh antirabbit IgG, while cytoplasmic prekeratin was identified by FITC anti-guinea-pig IgG.

Results

GROWTH CHARACTERISTICS AND FEATURES

Under the conditions of culture outlined 37 of the 53 membranes produced an outgrowth within the four-

Table 2 *Growth characteristics of ERMs in primary tissue culture*

	Number of ERMs	*Outgrowth within 4 weeks*	*Mean latent period in days (±standard error)*	*Stage III outgrowths*
Early ERMs	26	23 (88·5%)	2·67±0·3	16 (69·5%)
Late ERMs	27	14 (51·9%)	5·79±0·5	4 (28·6%)
Early vs late		$p<0·01$ (χ^2 test)	$p<0·01$ (Student's *t* test)	$p<0·05$ (χ^2 test)

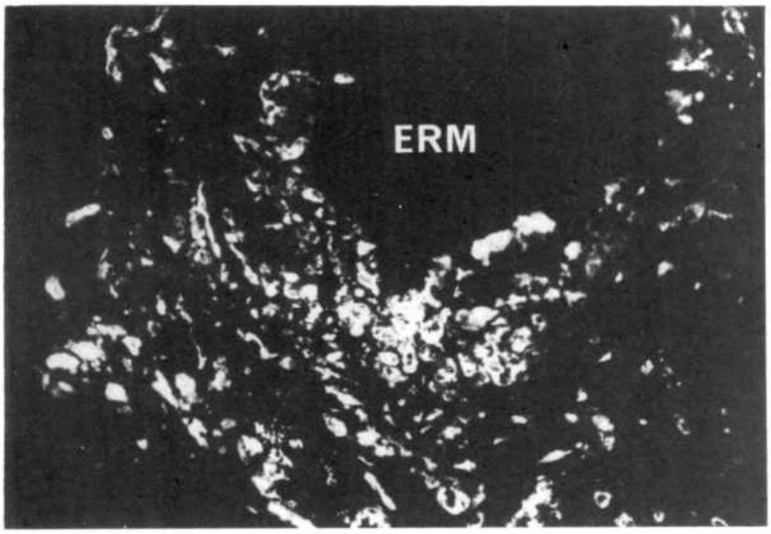


Fig. 3 *Antiactin indirect immunostaining with Rh conjugated to the second antibody of a cellular outgrowth from an epiretinal membrane (ERM) showing variable actin staining. The ERM does not fluoresce and therefore cannot be seen.* ×*100.*

week period (Table 2). The cells which grew from the ERMs were of variable appearance including spindle-shaped, plate-like, stellate, and ovoid cells (Fig. 1). There was a statistically significant difference between early and late ERMs in respect of viability (i.e., the numbers of explants yielding cells), latency (i.e., the time period prior to outgrowth of cells), and exuberance of outgrowth (i.e., the numbers of explants producing packed or stage 3 cultures) (Table 2).

IMMUNOHISTOCHEMISTRY AND TEM

Antiactin immunostaining highlighted the presence of contractile proteins within the ERM cells growing in tissue culture (Fig. 3). There was variability in the intensity of staining (Fig. 3) and in the pattern of staining, which was either reticular or diffuse (Fig. 4A, B). There was no pronounced reduction in antiactin staining after detergent treatment, and cytoplasmic actin was still prominent following exposure to ATP, though the staining pattern was always diffuse.

Among the growing cells antiprekeratin immunostaining showed the presence of epithelial cells interspersed between non-epithelial cells (Fig. 5). Double immunostaining illustrated cytoplasmic actin in both prekeratin-positive and prekeratin-negative cells, with no demonstrable difference between these cell types (Fig. 6A). Closer examination of cells which stained positively with both antisera revealed a difference in the distribution of the two antigens; the actin-rich elements were spread throughout the cytoplasm, whereas prekeratin was concentrated around the cell nucleus (Fig. 6B).

Electron microscopy confirmed the presence of

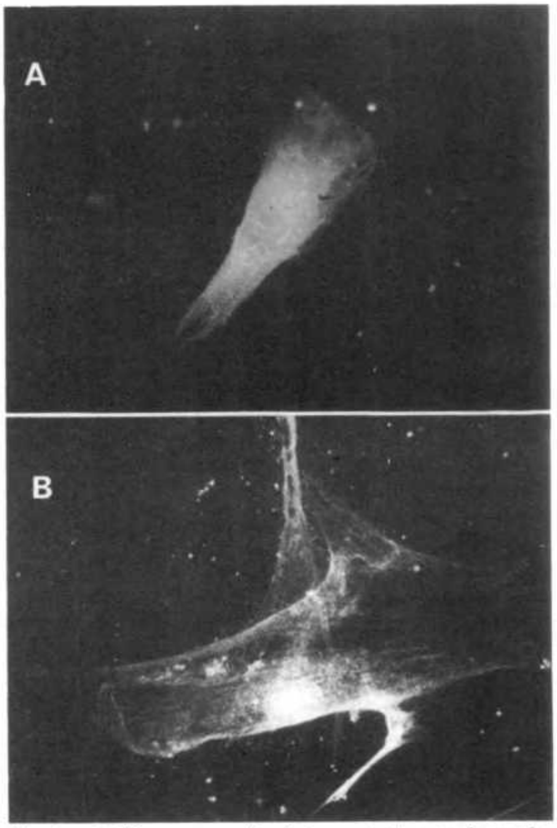


Fig. 4 *A diffuse pattern of actin is seen in the cytoplasm of a cultured ERM cell* (A) *whereas the pattern is reticular in another cell* (B) (FITC). ×*600.*

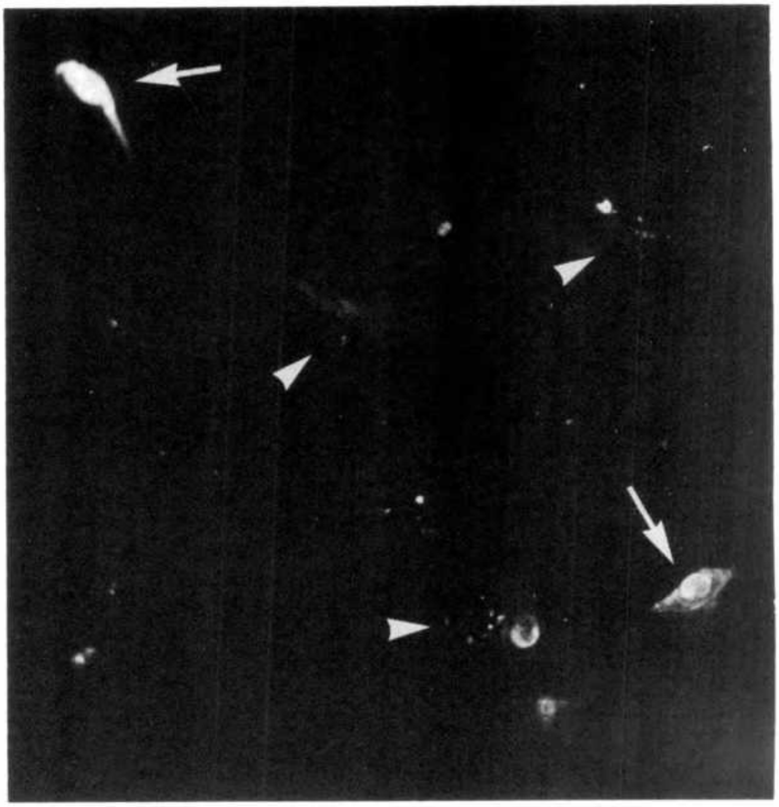


Fig. 5 *Positive (arrows) and negative (arrowheads) cells in an ERM culture after staining with antiprekeratin (FITC). ×400.*

cytoplasmic microfilaments (4–6 nm in diameter) in the cytoplasm of cells both within the ERM explant (Fig. 7) and growing in the culture flask. Microfilaments were abundant in some cells but difficult to find in others.

ATP ASSAY

The MgATP assay was more easily conducted on intact cells than on detergent treated cells because cell outlines could be seen more clearly (Fig. 8). Each of the 44 detergent treated cells had a reduced surface area after one hour's exposure to ATP, but there was marked variation in response between cells, ranging from as little as 7% to as much as 66% (Fig. 9). The mean area reduction was approximately 30% and significant by the paired *t* test ($p<0{\cdot}001$) (Table 3). Most of the reduction in surface area took place in the first 10 minutes of exposure to ATP (Fig. 10A, B). Of these 44 detergent treated cells 26 were prekeratin positive (Fig. 11), 11 were prekeratin negative and seven could not be identified after ATP assay because they were washed off during processing for indirect immunostaining. Table 3 also shows that the decrease in surface area after one hour was not significantly different in the three groups (i.e., in prekeratin-positive cells, prekeratin-negative cells, and unidentified cells) by Student's *t* test. The response of individual cells to ATP was as inconsistent in the prekeratin-positive group as it was for the whole series of cells (ranging from 7% to 50% reduction in area).

Of the 47 cells exposed to ATP without prior treatment with detergent (i.e., intact cells) all but one responded with a decrease in surface area (Fig. 12). Over a one-hour period the response was again variable (ranging from −1% to 65% with a mean of 34%), and most of the reduction once again took place in the first 10 minutes (Fig. 10A). The reduction in area was significant by the paired *t* test (Table 4) but was not significantly different from the reduction in area recorded from detergent treated cells (*t* test). Of these 47 intact cells, 18 were prekeratin-positive, nine were prekeratin-negative, and 20 could not be identified (Table 4). The decrease in area of the prekeratin-positive cells ranged from −1% to 50%, but there was no significant difference in the degree of response between prekeratin-positive, prekeratinegative, and unidentified cells (Table 4).

The average reduction in area of 48 cells from early membranes was 30% (±1·9%) and of 43 cells from

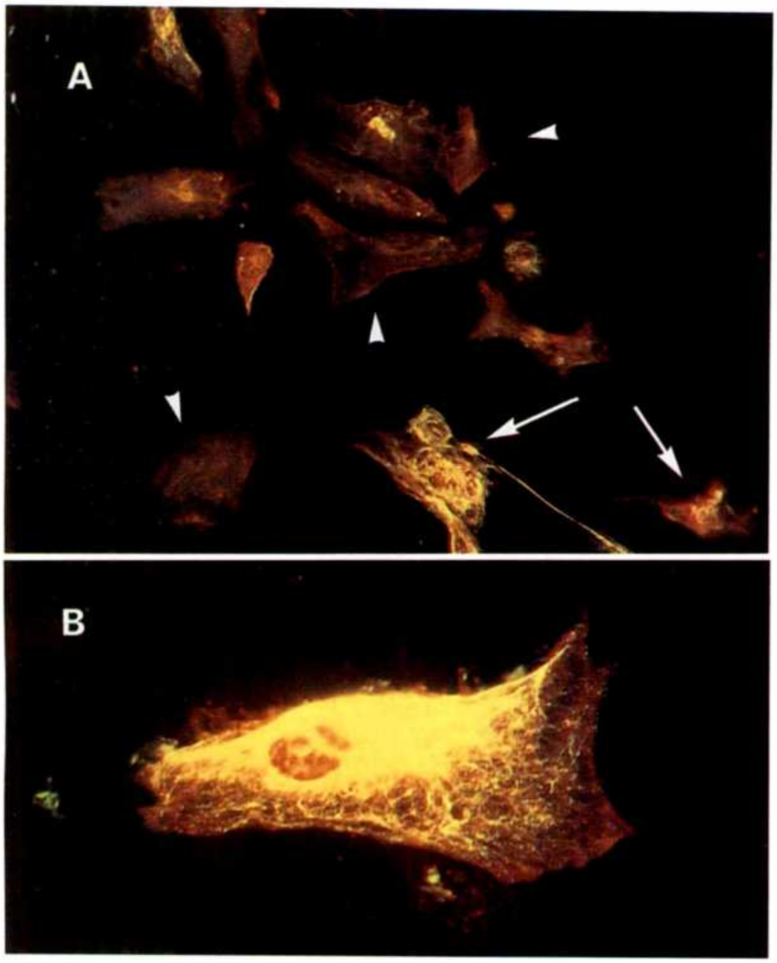


Fig. 6 *Prekeratin (FITC, green) and actin (Rh, red) double staining of an ERM culture.* A: *Prekeratin-negative cells (arrowheads) have a variable intensity of red. Prekeratin-positive cells (arrows) show some green, some red and also yellow where the prekeratin and actin fluorescence coincide (×300).* B: *A prekeratin-positive cell at higher power showing the distribution of prekeratin and actin (×750).*

late membranes was 34% (±2·6%). There was no significant difference between these two groups by Student's *t* test ($p > 0·05$).

Discussion

The features and growth characteristics of ERMs in culture confirmed the findings of a previous report from our laboratory.[7] Membranes with a clinical age of less than four months (described as early ERMs) had a greater propensity to grow, and to grow after a shorter latent period, than late ERMs (i.e., those of over four months' clinical duration). That late ERMs contain fewer cells and more collagen[9,13] than early ERMs would in part help to explain the initial poor performance of the former. However, it should also be borne in mind that, even when growing, the cells of late ERMs were less exuberant than those of early ERMs. Thus it would seem likely that in the culture conditions we established the cells of late ERMs have a diminished potential for replication.

The cells which grew out from our ERM explants varied greatly in morphology (confirming previous reports[6-8] and reflecting in part their polyphyletic composition).[1-5] They also showed great variability in the amount of cytoplasmic actin as indicated by microfilaments on electron microscopy and by anti-actin immunofluorescence. This study also confirmed the variability of actin staining of cells *within* excised ERMs.[9,14] However, to what extent the content and distribution of actin in the cultured cells reflected that of the ERM cells from which they derived is uncertain. Prominent actin immunostaining has been shown to be a feature of the growing edge of rabbit skin fibroblasts in tissue culture and during the early migratory phase after intravitreal fibroblast injection.[15]

Exposure of cells to either glycerin or non-ionic

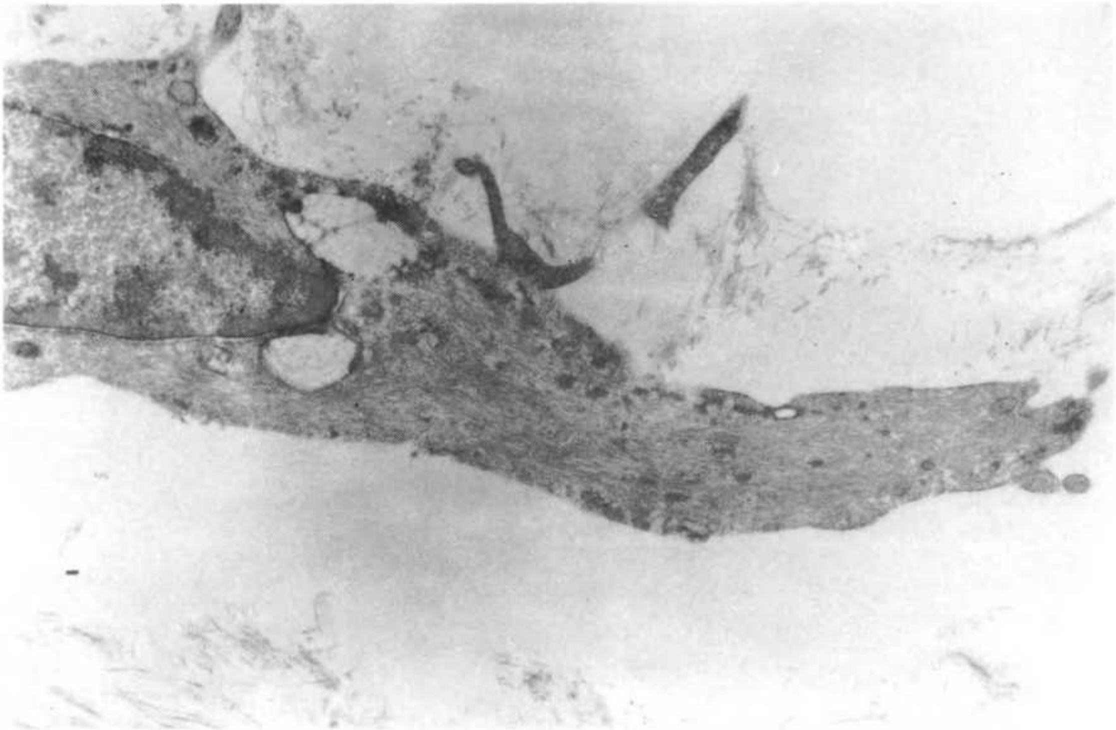


Fig. 7 *A cell in an ERM explant with prominent microfilaments in the cytoplasm as seen by transmission electron microscopy. ×15 000.*

detergents opens up cells and removes cytoplasmic constituents but leaves behind cytoplasmic filaments and the nucleus; these cell remnants are often referred to as cytoskeletons.[16 17] If the extraction procedure is conducted in a suitable buffer, then most of the contractile elements can be preserved.[12] The glycerin or detergent prepared cytoskeletons are freely permeable to electrolytes, drugs, and other chemicals. Indeed, the cytoskeletal preparations from a variety of cells (including amoebae, neutrophils, and fibroblasts) will decrease their surface area after exposure to ATP.[12 18-20] The decrease in surface

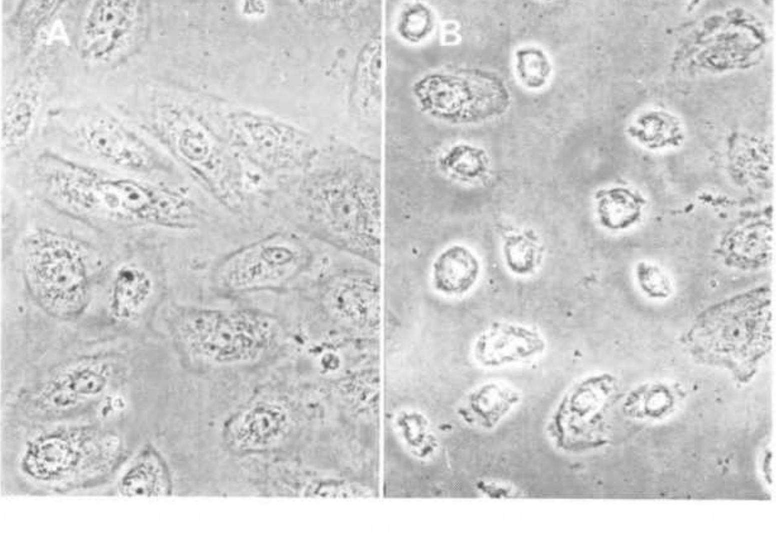


Fig. 8 *Area change of some intact cells from an ERM during ATP assay.* A: *The cells before adding ATP.* B: *The same cells after exposure to ATP for one hour. ×300.*

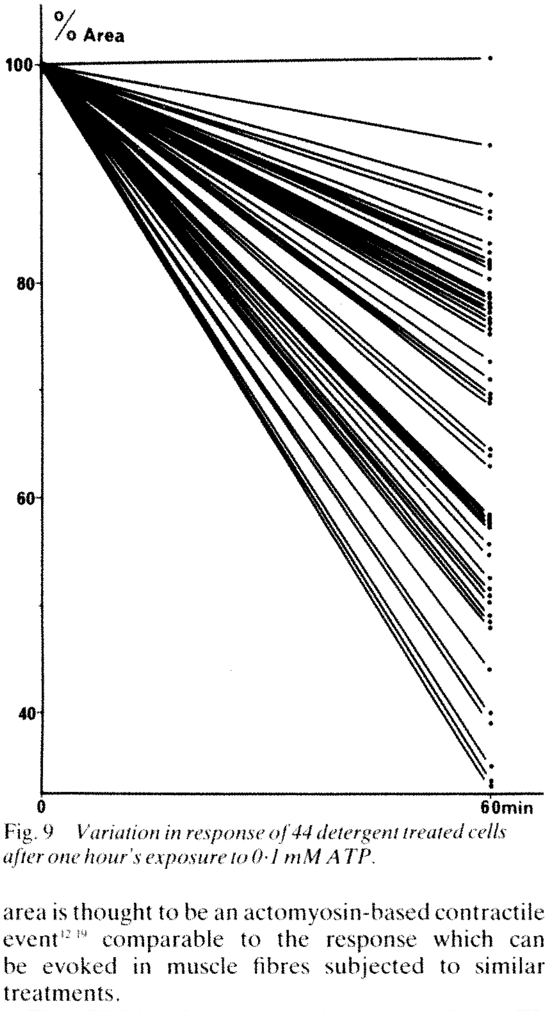


Fig. 9 *Variation in response of 44 detergent treated cells after one hour's exposure to 0·1 mM ATP.*

area is thought to be an actomyosin-based contractile event[12,19] comparable to the response which can be evoked in muscle fibres subjected to similar treatments.

That ERM cells contract when exposed to ATP has recently been shown by Yamashita and colleagues,[14] who used a glycerination procedure to produce cytoskeletons. We opted for Triton X-100 because glycerin treatment loosens the attachment of cells to the substrate much more than detergent treatment,[12,21] precluding subsequent immunostaining for actin or prekeratin. Glycerinated cytoskeletons also have the disadvantage that on contraction there is structural fragmentation so that the contraction is irreversible.[19] The Triton X-100 treated cytoskeletons decreased in area by some 30% in response to ATP over a period of one hour. Although most of the response took place in the first 10 minutes, the contraction was slower and less pronounced than that associated with glycerinated cytoskeletons[14] of ERM cells exposed to 30 times the concentration of ATP used in this study.

We were surprised to find that intact ERM cells (i.e., cells not exposed to detergent) also produced an average 34% reduction in area when exposed to ATP. It has generally been considered that glycerination or detergent treatment is a necessary prerequisite for an effective ATP response. Burridge[22] has emphasised the fact that cultured cells are generally strongly adherent to a rigid substrate (glass or plastic) and in such a condition can only express isometric forces; and furthermore that isotonic contraction will take place only if the cellular adhesion to the rigid culture plate is weakened by exposure to glycerin or detergent.[22] Certainly, cells well established in culture conditions (having been through several subcultures) are extremely adherent to their substrate; the tightly adherent cells have stress fibres (which are thick bundles of actin-rich microfilaments) and a well spread and flattened morphology.[22] The ERM cells of the present study were likely to be poorly adherent, being in primary culture and having only recently proliferated from the explant. Indeed our cells were relatively small and not flattened; for example, the prekeratin-positive cells had a surface area which was one-third that of fifth-passage cultured human retinal pigment epithelium (Boulton M, personal communication). Antiactin staining of the ERM cells showed a reticu-

Table 3 *Area change produced in detergent treated ERM cells by 0·1 mM ATP*

Cell type	*No. of cells*	*Exposure time (minutes)*	*Area of cells (in μm²) (mean ± SEM)*	*% of original area (mean ± SEM)*	*Paired t test*
Prekeratin-positive	26	0	224·7±20·9	100	—
		10	180·6±17·3	80·3±2·2	<0·001
		60	158·5±14·8	70·6±2·4	<0·001
Prekeratin-negative	11	0	201·2±26·5	100	—
		10	162·7±20·3	80·9±3·7	<0·01
		60	143·5±19·1	71·4±3·1	<0·01
Unidentified	7	0	341·4±54·2	100	—
		10	251·9±37·8	73·8±5·6	<0·05
		60	223·8±40·9	65·6±6·9	<0·05
All cells	44	0	237·4±17·5	100	—
		10	186·9±13·4	78·7±3·7	<0·001
		60	164·8±12·3	69·4±1·9	<0·001

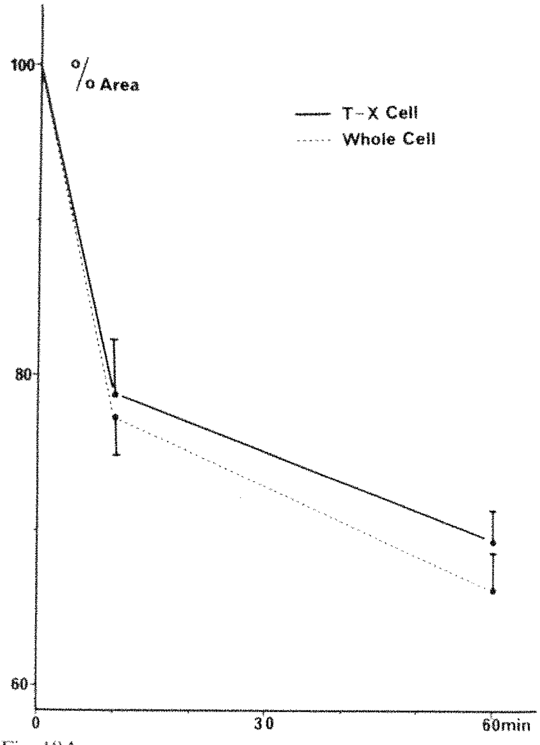


Fig. 10A

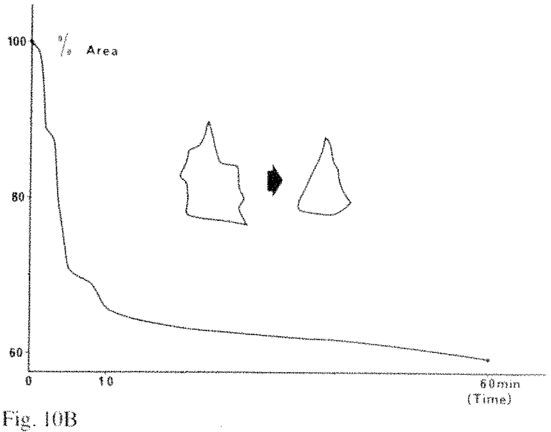


Fig. 10B

Fig. 10 *Most change in area took place in the first 10 minutes. A: Area change produced in both detergent treated and intact cells by 0·1 mM ATP. T-X = Triton-X treated.*

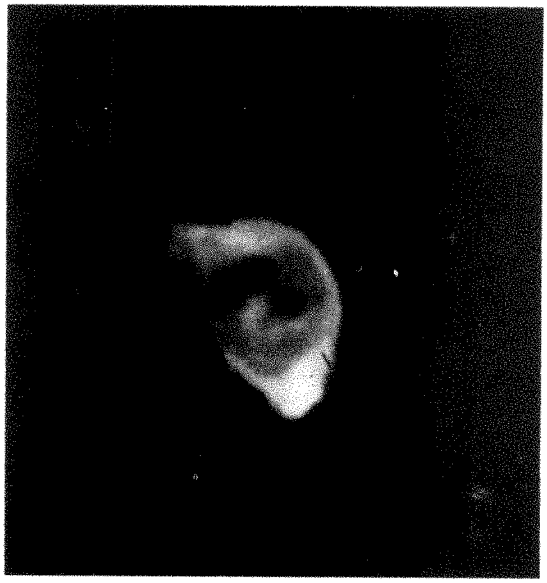


Fig. 11 *A prekeratin-positive ERM cell after detergent treatment and ATP assay (FOTC). ×800.*

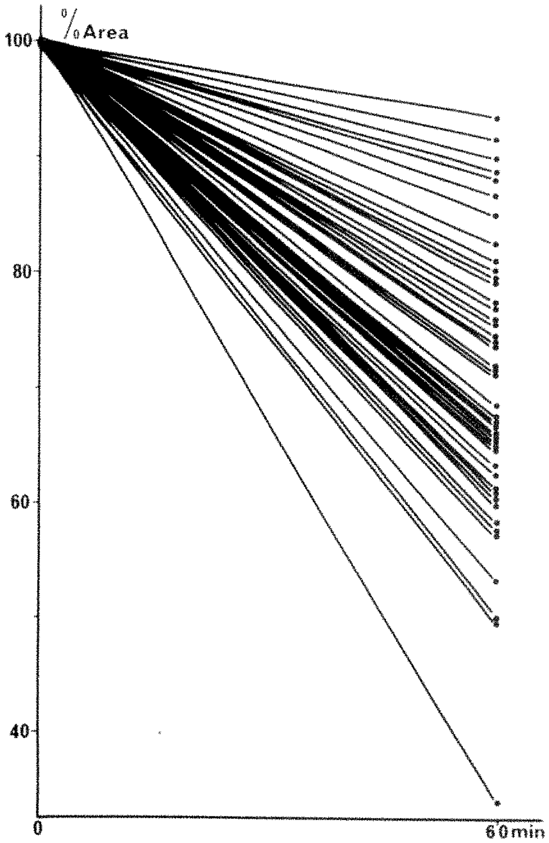


Fig. 12 *Variation in response of 47 intact cells after one hour's exposure to 0·1 mM ATP.*

Table 4 *Area change produced in intact ERM cells by 0·1 mM ATP*

Cell type	*No. of cells*	*Exposure time (minutes)*	*Area of cells (in μm^2) (mean±SEM)*	*% of original area (mean±SEM)*	*Paired t test*
Prekeratin-positive	18	0	379·4±91·6	100	—
		10	306·3±79·9	79·3±3·8	<0·001
		60	284·5±78·9	70·8±3·9	<0·001
Prekeratin-negative	9	0	317·7±71·6	100	—
		10	250·7±68·7	75·8±6·3	<0·01
		60	213.9±69·5	58·6±7·2	<0·01
Unidentified	20	0	379·3±59·1	100	—
		10	306·9±54·3	76·3±3·6	<0·001
		60	263·3±48·8	65·5±3·5	<0·001
All cells	47	0	367·5±44·6	100	—
		10	295·9±39·9	77·3±2·4	<0·001
		60	261·9±38·4	66·2±2·5	<0·001

lar pattern in the cytoplasm of some cells, but the fine threads of actin-positive fluorescence were not stress fibres; stress fibres are much thicker structures.[17] Their small size and the absence of stress fibres would make it unlikely that ERM cells had particularly tenacious attachments and in part helps to explain their ability to respond to ATP. Detailed investigation is required before the ATP contraction associated with intact ERM cells in primary culture is fully understood. Nevertheless there are distinct advantages in working with intact cells; for example, there is no possibility of elution of contractile elements, and the outline of an intact cell is far easier to measure than that of a cytoskeleton during the ATP assay.

A total of 91 intact cells and cytoskeletons were analysed during ATP exposure and all but one contracted to some extent. The variation in response between cells or their cytoskeletons was so pronounced that we suspected that this was related to the different clinical ages of ERMs or to cell type. However, immunostaining for cytokeratins (after the contraction run) showed that the response of epithelial cells was just as wide ranging as that of the non-epithelial cells. Given the similarity of response of intact epithelial cells and epithelial cytoskeletons, it is unlikely we were dealing with an artefact relating to assaying procedures. More probably we were dealing with differences in the cells metabolism or behaviour at the time of assay. In particular the organisation and amount of actin appeared to vary in both the epithelial and non-epithelial groups of cells.

This is the first demonstration that ERM-derived cells which are undoubtedly epithelial can contract. Since the early work of Machemer[2 23] retinal pigment epithelial cells have been especially implicated in the formation and tractional activities of ERMs. However, the contraction of epithelial cells was no greater than that of other cells in our ERMs supporting our view, expressed elsewhere,[5 24] that the role of retinal pigment epithelial cells has perhaps been overemphasised. Our histochemistry, following the ATP assay, showed that 44 out of 64 cells were prekeratin-positive. This high proportion of epithelial cells may reflect their preferential growth in our culture conditions, or preferential selection for assay because of their clearly defined borders and contact inhibition,[7] rather than their prevalence in situ.

We hope that the single cell assay can be used in future for further evaluation of the contractility of the different types of cell which can be grown from epiretinal membranes. It is intended that our assay be used to evaluate smooth muscle relaxant drugs which may have a role in controlling tractional activity in situ.

This work has been supported by the Wellcome Trust (grant no. 10998/1.5) and in part by the TFC Frost Charity Trust. We thank Mr P K Leaver, Mr R J Cooling, and Mr Z Gregor, who provided many of the specimens, and Mrs P Goodwin for secretarial assistance.

References

1 Van Horn DL, Aaberg TM, Machemer R. Glial cell proliferation in human retinal detachment with massive periretinal proliferation. *Am J Ophthalmol* 1977; 84:383–93.

2 Machemer R, Van Horn DL, Aaberg TM. Pigment epithelial proliferation in human retinal detachment with massive periretinal proliferation. *Am J Ophthalmol* 1978; 85: 181–91.

3 Kampik A, Kenyon KR, Michels RG, Green WR, de la Cruz ZC. Epiretinal and vitreous membranes: comparative study of 56 cases. *Arch Ophthalmol* 1981; 99: 1445–54.

4 Hiscott PS, Grierson I, Trombetta CJ, Rahi AHS, Marshall J McLeod D. Retinal and epiretinal glia: an immunohistochemical study. *Br J Ophthalmol* 1984; 68: 698–707.

5 Hiscott PS, Grierson I, McLeod D. Retinal pigment epithelial cells in epiretinal membranes: an immunohistochemical study. *Br J Ophthalmol* 1984; 68: 708–15.

6 Newsome DA, Rodrigues MM, Machemer R. Human massive periretinal proliferation: in vitro characteristics of cellular components. *Arch Ophthalmol* 1981; 99: 873–80.

7 Hiscott PS, Grierson I, Hitchins CA, Rahi AHS, McLeod D. Epiretinal membranes in vitro. *Trans Ophthalmol Soc UK* 1983; 103: 89–102.

8 Yamashita H, Hori S, Kitano S, Ishii Y, Masuda K. Glial cells in culture of preretinal membrane of proliferative vitreoretinopathy. *Jpn J Ophthalmol* 1985; **29:** 42–53.

9 Hiscott PS, Grierson I, McLeod D. Natural history of fibrocellular epiretinal membranes: a quantitative, autoradiographic and immunohistochemical study. *Br J Ophthalmol* 1985; **69:** 810–23.

10 Gabbiani G, Ryan GB, Majno G. Presence of modified fibroblasts in granulation tissue and their possible role in wound contraction. *Experimentia* 1971; **15:** 549–50.

11 Gabbiani G, Hirschel BJ, Ryan GB, Statkov PR, Majno G. Granulation tissue as a contractile organ: a study of structure and function. *J Exp Med* 1972; **135:** 719–34.

12 Masuda H, Owaribe K, Hatano S. Contraction of triton-treated culture cells. *Exp Cell Res* 1983; **143:** 79–90.

13 Constable IL, Tolentino FI, Donovan RH, Schepens CL. Clinicopathologic correlation of vitreous membranes. In: Pruett RC, Regan CDJ, eds. *Retina congress*. New York: Appleton-Century-Crofts, 1974: 245–57.

14 Yamashita H, Hori S, Masuda K. Microfilaments in preretinal membrane cells of proliferative vitreoretinopathy. *Jpn J Ophthalmol* 1985; **29:** 394–405.

15 Grierson I, Rahi AHS. Structural basis of contraction in vitreal fibrous membranes. *Br J Ophthalmol* 1981; **65:** 737–49.

16 Osborn M, Weber K. The detergent-resistant cytoskeleton of tissue culture cells includes the nucleus and the microfilament bundles. *Exp Cell Res* 1977; **106:** 339–49.

17 Kries TE, Birchmeier W. Stress fiber sarcomeres of fibroblasts are contractile. *Cell* 1980; **22:** 555–61.

18 Simard-Duquesne N, Coulliard P. Amoeboid movement I: reactivation of glycerinated models of amoeba proteins with adenosine triphosphate. *Exp Cell Res* 1962; **28:** 85–91.

19 Norberg B. Amoeboid movements and cytoplasmic fragmentation of glycerinated leukocytes induced by ATP. *Exp Cell Res* 1970; **59:** 11–21.

20 Hsu LS, Becker EL. Volume decrease of glycerinated polymorphonuclear leukocytes induced by ATP and Ca2+. *Exp Cell Res* 1975; **91:** 469–73.

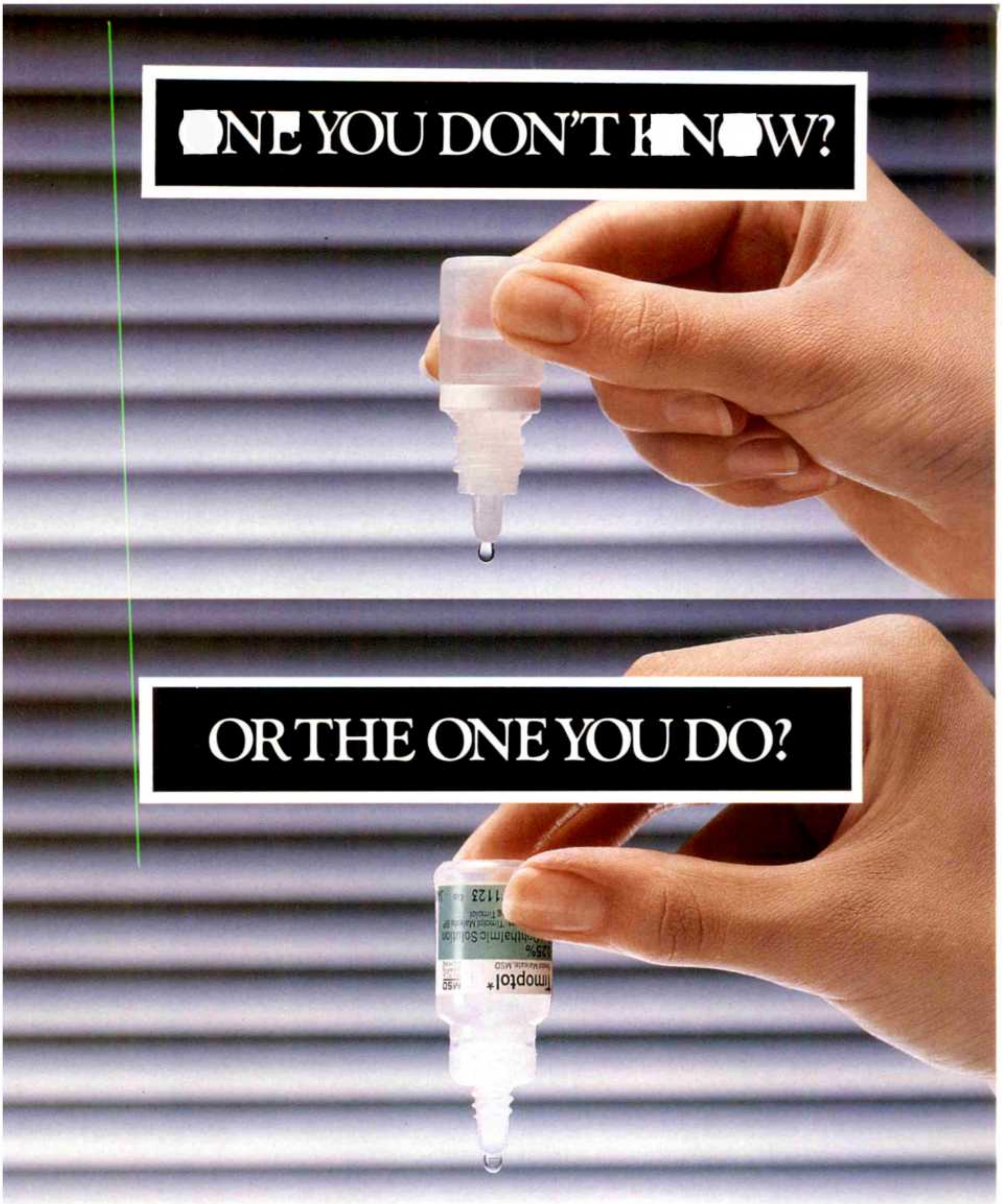
21 Grierson I, Millar LC, Jiang DY, *et al.* Anatomical and functional investigations of cytoskeletal elements in cultured bovine meshwork cells. *Invest Ophthalmol Vis Sci* 1986; **27:** 1318–30.

22 Burridge K. Are stress fibres contractile? *Nature* 1981; **294:** 691–2.

23 Machemer R, Laqua H. Pigment epithelial proliferation in retinal detachment (massive periretinal proliferation). *Am J Ophthalmol* 1975; **80:** 1–23.

24 McLeod D, Hiscott PS, Grierson I. Age-related cellular proliferation at the vitreoretinal juncture. *Eye* 1987; **1:** 263–81.

Accepted for publication 15 December 1986.



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References

1. Zimmerman, T. J., presented at: Int. Symposium on Glaucoma, XIII Int. Cong Ophthalmology, Kyoto, Japan, May 1978, 55-64.
2. Sponsel, W. E., *et al.*, *Brit. J. Ophthal.*, 1983, **67**, 220-227.
3. Sponsel, W. E., International Symposium on Glaucoma, Turin, 1986.
4. Katz, I. M., presented at: Int. Symposium on Glaucoma, XIII Int. Congr Ophthalmology, Kyoto, Japan, May 1978, 29.

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Visual failure in allergic aspergillus sinusitis: case report

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SUMMARY We present a case of rapid progressive unilateral visual loss in a 69-year-old woman who presented with facial pain, ipsilateral proptosis and restriction of eye movements, and nasal symptoms suggestive of sinusitis. A diagnosis of allergic aspergillus sinusitis was made on the basis of local histopathology and systemic features. Over a three-week period vision deteriorated to bare perception of light but showed a dramatic improvement to a level of 6/9 central vision on systemic steroid therapy. The mechanism of visual failure in the context of allergic aspergillus sinusitis and the therapeutic implications are discussed.

Allergic aspergillus sinusitis has recently been described[1,2] and appears to be analogous to allergic bronchopulmonary aspergillosis (ABPA). This similarity has important diagnostic and therapeutic implications which differ markedly from those associated with the more familiar infective aspergillosis of the sinuses and their adnexae.

We report a case of an elderly woman with characteristic paranasal sinus involvement and right orbital complications. A relentless decrease in right visual acuity to minimal light perception was arrested by recognition of the condition and prompt appropriate treatment. She rapidly regained, and has sustained, right acuity of 6/9 corrected during nine months' follow-up.

Case report

A previously fit and alert 69-year-old woman was admitted with a five-day history of headache, right periorbital and frontal pain, nausea, and progressive diminution of right visual acuity (VA) associated with right proptosis and a more recent onset of diplopia. She complained of three weeks of vague nasal congestion but denied nasal discharge.

Her general health had been good. She denied any history of asthma and/or chronic or recurrent respiratory symptoms. She denied atopy and significant allergies. She was a non-smoker and took no regular medication.

Examination on day one (D1) showed the right VA was approximately 6/24, the left 6/9. There was mild right periorbital swelling and proptosis, but little chemosis. She had a right relative afferent pupillary defect. Abduction and vertical deviations in abduction were moderately impaired on the right. The fundi were normal; in particular the right disc was not swollen or haemorrhagic, nor were the right retinal veins engorged.

The patient was afebrile, with leucocytes $7 \cdot 9 \times 10^9/l$, and erythrocyte sedimentation rate 32 mm in the first hour. The chest *x*-ray was normal. Skull *x*-rays showed clouded ethmoidal and frontal sinuses. Cranial CT confirmed soft tissue density in the ethmoidal sinuses and fluid in the sphenoid sinus, and right proptosis associated with increases in the orbital soft tissue density. There was no specific abnormality of the optic nerves nor of the optic canals.

On D2 an external ethmoidectomy and sphenoidotomy was performed via the right medial orbital wall. A large volume of mucoid granulation tissue was removed from the ethmoid and sphenoidal sinuses. Gram staining revealed no organisms. Pus cells were abundant, but culture failed to produce any significant growth. Further fungal studies were undertaken and later produced no growth.

Treatment continued with flucloxacillin 1 g 4-hourly intravenously, amoxycillin 1 g 4-hourly intravenously, gentamicin 60 mg 6-hourly intravenously, and neosynephrine nasal spray 6-hourly.

Postoperatively her condition failed to improve. On D8 the right VA was minimal light perception

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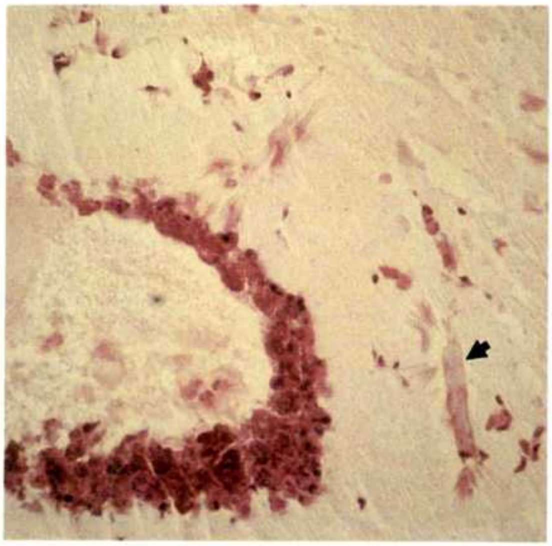


Fig. 1 *High-power view of paranasal drainage specimen showing a characteristic strip of inspissated eosinophils and a large Charcot-Leyden crystal (arrowed) in a mucinous background. Haematoxylin-eosin.*

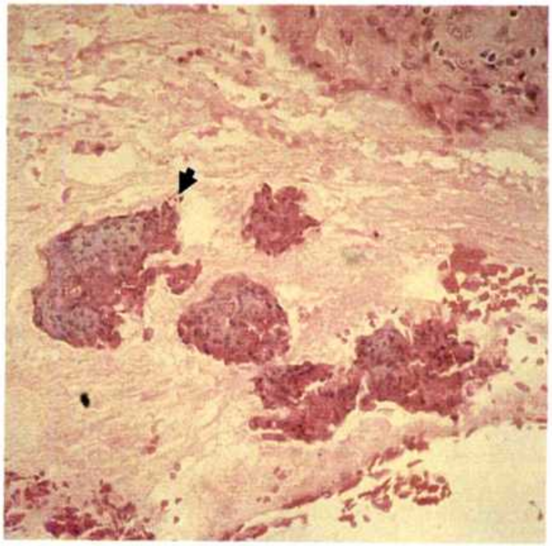


Fig. 2 *High-power view of paranasal drainage specimen showing an angulated cluster of eosinophils (arrowed) suggestive of fragmentation of a larger mass. Haematoxylin-eosin.*

with an absolute afferent pupil defect. The proptosis (19 mm/R, 14 mm/L) and mild periorbital oedema persisted. The right eye was exotropic and hypertropic with minimal ductions. The fundal findings remained normal.

A repeated cranial CT on that day revealed large amounts of fluid in maxillary, ethmoid, and sphenoid sinuses, with signs of mucosal thickening. The operative loss of the right lateral ethmoidal wall was noted. The right medial rectus was laterally displaced, and increases in orbital soft tissue density persisted. A differential full blood count showed leucocytes $6{\cdot}7\times10^9$/l with 9% eosinophils.

Antibiotic therapy was changed to cephalothin 1 g 4-hourly intravenously and metronidazole 200 mg 6-hourly by mouth. Again there was no significant clinical improvement.

On D12 histopathology suggested a diagnosis of allergic aspergillus sinusitis. The operative specimens revealed mucous masses surrounded by respiratory mucosa. In the mucous were Charcot-Leyden crystals associated with clusters and long strips of inspissated eosinophils. These clusters were sharply angulated, suggesting that they had broken off from a larger mass. Although no fungal filaments were demonstrated, the appearance was characteristic of the changes found in allergic bronchopulmonary aspergillosis[3] and allergic aspergillus sinusitis.[1 2]

Antibiotics were stopped and prednisone 15 mg twice daily by mouth was begun on D13. Metronidazole continued until D15. Despite corticosteroid therapy, *Aspergillus fumigatus* serum precipitins were requested and returned negative results at both high (20 g/l) and low (2 g/l) concentrations. Serum IgE levels were not measured.

The patient noted an immediate improvement. On D18, she could count fingers poorly and had developed a right relative afferent pupil defect. Her right ductions improved and right exotropia decreased. On D22 the right VA was 6/18 corrected. The afferent defect had resolved. Ductions were only mildly impaired and the right visual field (Bjerrum) was normal. Prednisone was decreased to 12·5 mg twice daily. On D32 the right VA was 6/12 corrected. This further improved to 6/9 corrected by D41 and has remained stable since.

Checkerboard visual evoked responses performed on D41 showed a normal left response but increased latency (+122 ms) and decreased amplitude on the right consistent with a persistent right optic neuropathy.

At 12 months she was currently asymptomatic and on prednisone 5 mg twice daily.

Discussion

Unilateral visual loss in the elderly is most often acute and irreversible, owing to vascular events in the field of the ophthalmic artery. Progressive visual loss with pain and proptosis more often arises from optic nerve involvement in orbital cellulitis, either primary or secondary to paranasal sinus infection, which may be due to a multiplicity of causative organisms including the potentially lethal mucormycoses associated with diabetes mellitus. Tumour, either primary or secondary of the orbit, paranasal sinuses, nasopharynx, or parasellar regions may also present in this way, though pain is less often a feature—pain occurring more frequently in pseudotumour.

Careful history taking and radiological investigations including CT scanning will usually provide evidence for the diagnosis. In the present case the history was not suggestive of a vascular cause, and the pattern of involvement of multiple sinuses made malignancy unlikely.

In the context of paranasal sinusitis impaired vision is normally an indication for surgical drainage, at which time both microbiological and histopathological specimens may be obtained. Aeration of the ethmoids associated with pneumatisation of the optic canal or sphenoidal mucocele involving the optic canal can usually be demonstrated by careful radiological examination. Where there is no bony involvement in the presence of a systemic eosinophilia, the diagnosis of allergic aspergillus sinusitis should be considered. In the past, visual failure has not been regarded as a serious threat in allergic aspergillus sinusitis, though this case illustrates that the diagnosis should be considered when culture of organisms is negative and a visual deficit progresses despite surgical drainage of the paranasal sinuses.

Allergic aspergillus sinusitis[1 2] is a very different entity to the uncommon but more familiar infective aspergillosis of the paranasal sinuses and/or orbit. Chronic sinusitis is mainly due to aerobic and anaerobic bacterial infection. When, infrequently, true fungal infection occurs, it has been subdivided into invasive and non-invasive forms.

The invasive form has a spectrum of activity from a slow and relatively asymptomatic form to a fulminant one seen in the debilitated and immunosuppressed, where 60% mortality has been reported.[4 5] Single sinus involvement occurs in more than half these cases.[1 2 4] Histologically there is marked tissue necrosis with granulomatous and fibrotic reactions associated with abundant characteristic fungal hyphae. The non-invasive form is equivalent to the pulmonary mycetoma. It usually involves a single sinus, presenting a dense tangled mass of hyphae associated with little inflammatory reaction. The treatment of both types involves local surgical excision and antifungal agents. In each case hyphae are numerous; in neither is mucin production a major feature.

Allergic aspergillus sinusitis has recently been described as a new and distinct clinicopathological entity analogous to allergic bronchopulmonary aspergillosis (ABPA).[1 2] The latter has long been recognised as an aspergillus hypersensitivity manifestation of the bronchopulmonary tree with specific histopathological features and treatment implications. Allergic aspergillus sinusitis, occurring in the paranasal sinuses without, necessarily, concomitant lung involvement, shares these features—opacification of multiple sinuses with distinct mucinous material containing eosinophils, Charcot-Leyden crystals, and fungal hyphae.[1] This material is characterised by aggregation of necrotic inspissated eosinophils lying in thin strips or clusters that frequently show angulation suggestive of cleavage from a larger mass.[3] The background mucous contains nuclear debris, sloughed respiratory mucosal cells, free eosinophil granules, and Charcot-Leyden crystals. These crystals, hexagonal in cross section, bipyramidal in longitudinal section, and of variable size, form from aggregation of eosinophil granules.[2] This constellation of findings is indicative of 'allergic mucin'.

On histological grounds and in terms of response to treatment we believe this to be such a case despite certain clinical differences. In Katzenstein's retrospective series, age range 13–48, most patients were young adults with a history of asthma and chronic sinus involvement. All had multiple sinus involvement, and most a normal chest *x*-ray. Several had undergone recurrent surgical drainage procedures. Our patient is elderly. She denies chronic nasal or respiratory problems and related surgery. However, it is noteworthy that she presented late, with primarily ocular symptoms. Her failure to respond to surgical drainage and intensive antibiotic therapy, worrisome at the time, is typical of the condition.

The diagnosis was made on histopathological appearances. Culture of operative specimens was unhelpful. A tell-tale eosinophilia within a normal white cell count was evident when sought. 'Allergic mucin"[1 2] was abundant in the specimens. Jelihovsky[3] reports its most distinctive feature as inspissated, often angular, clusters of eosinophils, within some of which fungal hyphae are found. In one reported case, submitted to 10 drainage procedures, allergic mucin was found on three occasions, only one of which contained identifiable hyphae. As the hyphae are not numerous, unlike infective aspergillosis, sampling difficulty may be the explanation. It is also possible that an allergen other than aspergillus is present.[1]

The mechanism of visual loss in this case is not certain, and we have been unable to find reports of such loss in this condition. It may be that the orbital inflammatory changes, sufficient to cause proptosis and minimal ductions, compress the optic nerve proximally to produce an 'orbital apex syndrome', such as that seen in dysthyroid optic neuropathy. However, the recti, with the exception of the medial rectus, were not grossly enlarged on CT. It is also possible that the right optic nerve was directly involved in the orbital and paranasal inflammation. The latter possibility is in keeping with the impressive response to steroids. It is also more likely on the basis of the increased latency and diminished amplitude of the checkerboard VEP.

There are no prospective data on optimal therapy for allergic aspergillus sinusitis. The remarkable and sustained recovery in this case reinforces the primary role of corticosteroids. This is consistent with Safirstein's report of a young woman with proved ABPA and chronic sinusitis now presumed to be allergic aspergillus sinusitis.[6] The sinus-related histopathology was not described. She experienced a 'dramatic' and simultaneous improvement of lung and nasal conditions on prednisone (30 mg), and exacerbations thereof on cessation. These results with corticosteroids are in sharp contrast to those achieved with surgical drainage and antifungal agents, where multiple recurrences are common.

The role of serology in diagnosis is not clear. Our negative results to *Aspergillus fumigatus* precipitins were complicated by concomitant steroid therapy. Serum IgE was not tested. Both these tests are useful but not absolute in ABPA and were positive in the majority of those tested in Katzenstein and colleagues' series.[1] It is clear that relevant peripheral blood studies, differential leucocyte counts for eosinophilia, and tests for IgE and precipitins, should be done early in investigation of these patients.

In conclusion, we present what we believe to be a case of allergic aspergillus sinusitis with right orbital complications and progressive visual loss. The patient's age and previous respiratory history are atypical. Her poor response to surgical drainage is typical. The histopathological features of 'allergic mucin' are characteristic, while the absence of identifiable fungal hyphae is not unusual. The peripheral eosinophilia should have been recognised earlier. Most importantly, there was an immediate and sustained recovery from blindness to comfortable reading vision with corticosteroid therapy.

With sophisticated radiological imaging to confirm the diagnosis in the presence of a systemic eosinophilia and positive serology, a presumptive diagnosis of allergic aspergillus sinusitis followed by a trial of steroid therapy without formal surgical exploration is, we believe, a reasonable approach to management. Should doubt exist, surgical intervention provides both appropriate drainage for true paranasal sinus infection and microbiological and histological specimens for pathological diagnosis.

Allergic aspergillus sinusitis is a newly recognised and uncommon condition. Its association with reversible visual loss is important. In our present state of knowledge nature seems capricious in choosing to affect certain individuals. While prednisone appears to offer dramatic improvement, so too may steroids initially attenuate ocular and paranasal tumours. We believe that allergic aspergillus sinusitis warrants a wider press and higher index of suspicion. Further information on optimal therapy and long-term follow up would be helpful.

NOTE ADDED IN PROOF. At 22 months follow-up central acuity remains 6/9 with no indication of visual deterioration on therapy with prednisone 2 mg on alternate days.

We thank Dr Tatiana Jelihovsky for her histopathological diagnosis and relevant photographs.

References

1 Katzenstein A, Sale S, Greenberger P. Allergic aspergillus sinusitis: a newly recognised form of sinusitis. *J Allergy Clin Immunol* 1983; **72**: 89–93.

2 Katzenstein A, Sale S, Greenberger P. Pathologic findings in allergic aspergillus sinusitis. *Am J Surg Pathol* 1983; **7**: 439–43.

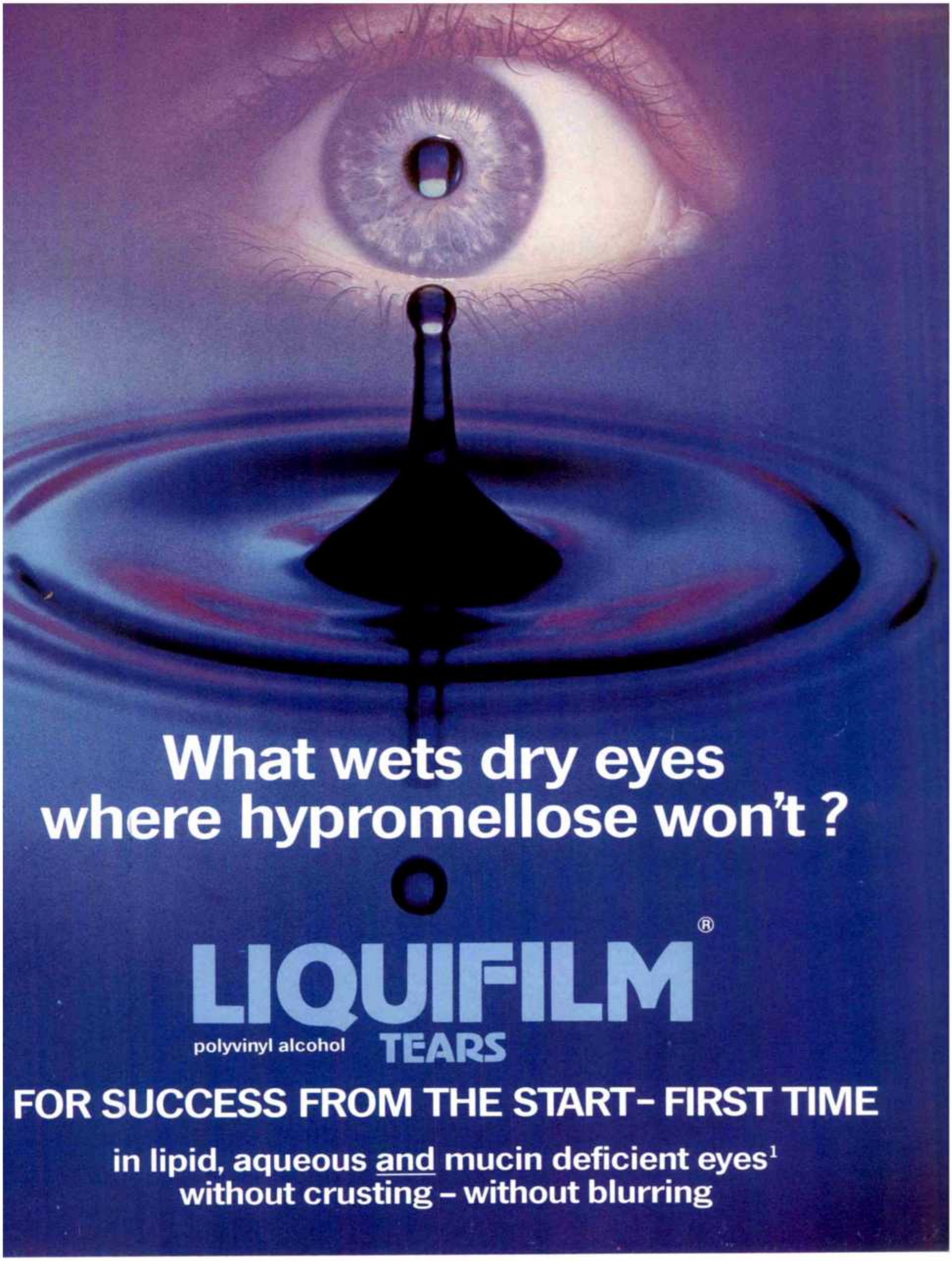
3 Jelihovsky T. The structure of bronchial plugs in mucoid impaction, bronchocentric granulomatosis and asthma. *Histopathology* 1983; **7**: 153–67.

4 Green WR, Font RL, Zimmerman LE. Aspergillosis of the orbit. *Arch Ophthalmol* 1969; **82**: 302–13.

5 Wolter JR. Diagnosis and management of orbital aspergillosis. *Ann Ophthalmol* 1976; **8**: 17–20.

6 Safirstein B. Allergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. *Chest* 1976; **70**: 788–90.

Accepted for publication 15 December 1986.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Reference 1. Kralian LM, American Journal of Optometry and Physiological Optics 1986; **63** (No. 4): 304-308.

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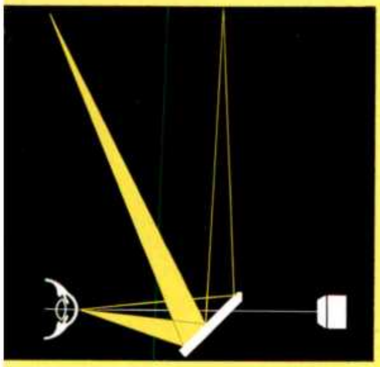

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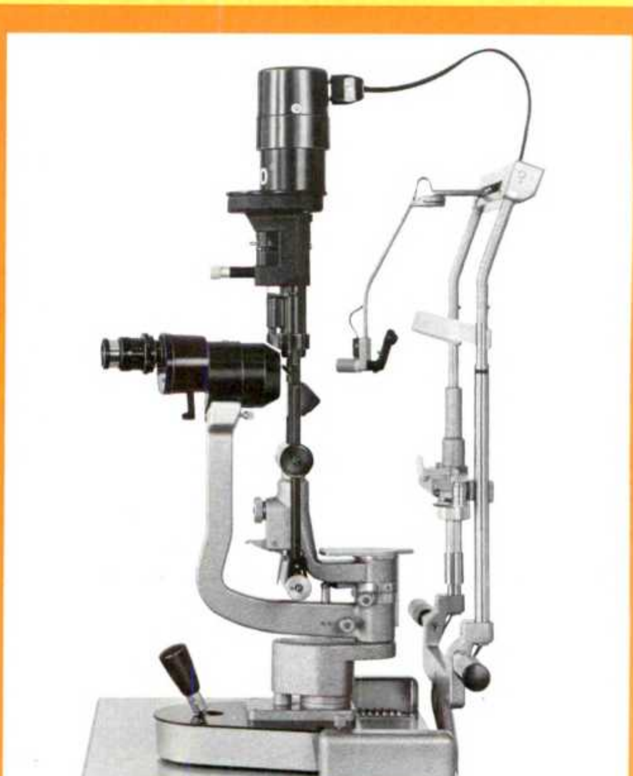

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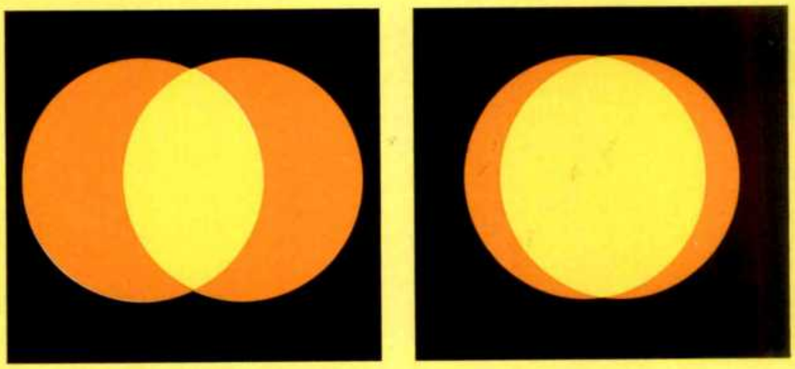

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British Journal of Ophthalmology, 1988, **72**, 131–133

Malignant melanoma of the choroid in a naevus of Ota

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SUMMARY A rare case of choroidal malignant melanoma in a naevus of Ota is described. This is the first reported case from Asia outside the Japanese population. This case illustrates the need for close observation of all pigmented lesions of the eye.

Naevus of Ota or 'Oculodermal melanocytosis' is a congenital hyperpigmentation of the facial skin in the distribution of the first and second divisions of the trigeminal nerve which is often associated with increased pigmentation of the various ocular structures.[1] Malignant change in the naevus of Ota is rare, and when involving the choroid it has been reported mostly in Caucasians.[2] Only four such cases have been seen in the Oriental population.[3]

We describe a case of choroidal malignant melanoma in the naevus of Ota in a Malay woman.

Case report

A 72-year-old Malay woman was admitted to the medical ward of the General Hospital, Kuala Lumpur, on 19 December 1984 with a one-week history of loss of weight and appetite, abdominal distension, and passing dark coloured urine. She also complained of slight watery discharge of her right eye on and off. She had been blind in the right eye for four years and had frequent episodes of ocular pain. Her right eyeball as well as right periocular skin had been pigmented since childhood.

On examination she looked emaciated, severely jaundiced, and had moderate ankle oedema. The abdomen was distended. Ascites was present along with a markedly enlarged liver, which was firm, nodular, and not tender. The spleen was palpable.

INVESTIGATIONS

Liver function tests confirmed severe hepatic damage. Tests for α-fetoprotein and hepatitis B surface antigen were negative. While she was being investigated for the cause of liver failure she was referred to the eye clinic because of her discharging right eye.

Ophthalmological findings. Light perception was absent in the right eye and she could only count fingers at 1 m with her left eye. Several irregular patches of bluish scleral pigmentation were visible in all quadrants. The right eyeball was slightly congested, and dilated episcleral vessels were prominent. Black episcleral nodules were also noted at the upper limbus as well as near the superior fornix. The lower two-thirds of the cornea was densely opaque. There was no outline of the pupil (Fig. 1). A fundus

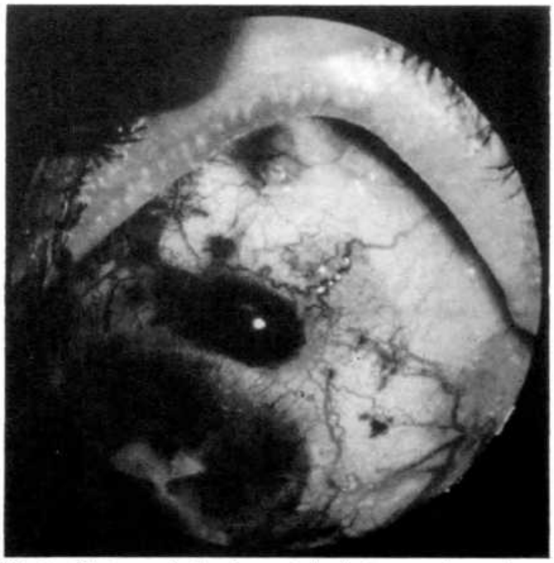

Fig. 1 *Photograph showing episcleral pigmentation and black nodule. Dilated subconjunctival vessels are also visible.*

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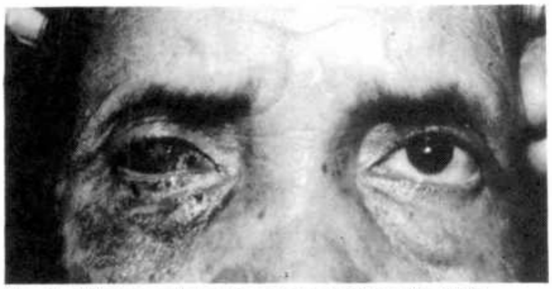


Fig. 2 *Photograph showing pigmentation of the right periocular skin.*

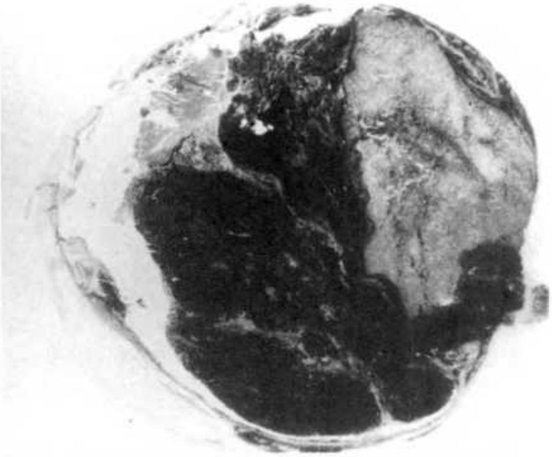


Fig. 3 *Photograph of the sectioned eyeball showing the tumour mass filling the vitreous cavity and invasion of the optic nerve.*

view was not possible and the eye felt hard to palpation. The left eye showed yellow discolouration of the sclera and the left lens was cataractous. No other abnormality was detected in the left eye.

Dermatological findings. Dark blue pigmentation of the skin involving the right upper and lower lids as well as part of the right cheek and right temple was present (Fig. 2).

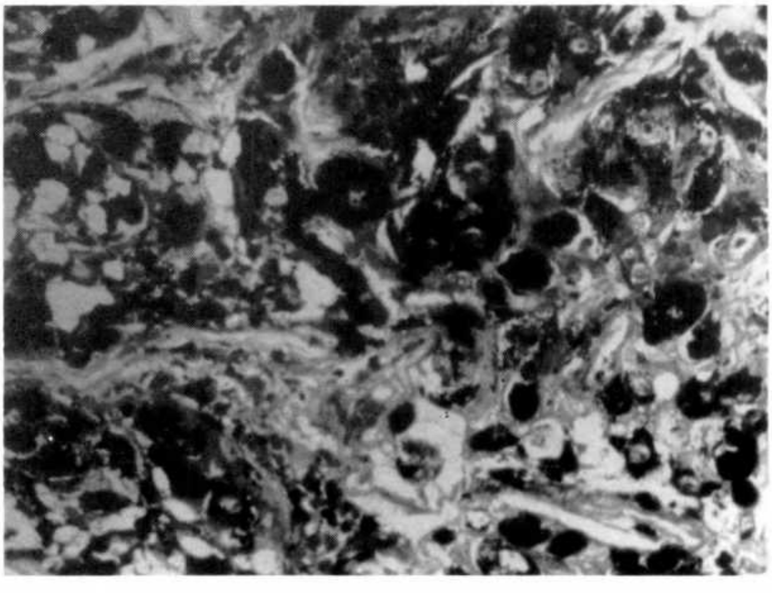
A clinical diagnosis of malignant melanoma in a naevus of Ota with metastasis in the liver was made. On further questioning the patient stated that she had attended the eye clinic four years previously for severe right visual loss. She was advised to have her right eye removed but had refused, and she defaulted from further follow-up. The presence of a raised, solid, pigmented lesion involving the right macular area and reaching the temporal edge of the right optic disc was recorded in her old case notes in the eye clinic.

The right eye was enucleated on 20 December 1984 and the patient died four days later. A post-mortem specimen of liver was taken.

PATHOLOGICAL FINDINGS

The enucleated eyeball measured 25×25×25 mm; the attached optic nerve was 7 mm in length and 5 mm in diameter. The lower part of the cornea was opaque. Multiple darkish nodules, the largest measuring 6×3×1 mm, were seen over the sclera. The eyeball was sectioned through the meridional plane. It was completely filled with a dark solid mass. There was infiltration of the optic nerve and sclera.

Fig. 4 *Photomicrograph showing the melanoma cells. H and E.*



The lens was displaced and fragmented at its periphery by infiltration of the dark mass. The anterior chamber was filled with tumour tissue (Fig. 3).

Microscopically pigmented dendritic melanocytes were found within the superficial sclera. The mass was composed mainly of polygonal malignant cells containing heavily pigmented cytoplasm and round nuclei with prominent nucleoli. Mitotic figures were frequently present. Large areas of necrosis were seen within the mass. There was infiltration of the sclera, angle structures, and the entire optic nerve by malignant cells (Fig. 4).

The histopathological diagnosis was malignant melanoma of epithelioid type. Histopathology of the liver material also showed melanoma cells.

Discussion

Malignant melanoma of the eye is rare in Orientals, though relatively common in Caucasians. All pigmented lesions of the eye in a white person are therefore closely watched for fear that they might become malignant at any time during the life of that individual. One such pigmented lesion of the eye is the naevus of Ota. Clinically and histologically the episclera and the choroid have been observed to be involved by the melanocytic process in almost all cases of oculodermal melanocytosis.[2] Malignant change in the naevus of Ota has been reported involving the skin,[4] choroid,[3 5-8] iris,[9] orbit,[10 11] and brain.[12]

Naevus of Ota is common in the Oriental population but malignant change in these cases is regarded as extremely rare. On the other hand naevus of Ota is considered to have a high potential for malignancy when it does occur on rare occasions in the white races.[2 13 14] It is generally recommended that a naevus of Ota in a white person should be kept under close observation. On the basis of the present report we suggest that, since malignant change is possible in naevus of Ota in an Oriental, all such cases should also be kept under observation.

Primary ocular malignancy as the cause of terminal illness in our patient was not recognised by the medical staff until she was seen by us. We feel that it is often not well appreciated in the Oriental population that widespread metastatic disease can result from primary neoplasm in the eye, and the result may be that the patient undergoes unnecessary invasive investigations. Lack of understanding of the nature of the disease in our patient prevented her from consenting to enucleation when malignancy was detected in her eye four years previously. We believe there is a great need to educate the public about diseases like treatable cancer.

We thank Encik Alias Manap for the photographic work and Puan Nurul Amani Mohd Danin for her secretarial help.

References

1 Fitzpatrick TB, Zeller R, Kukità A, Kitamura H. Ocular and dermal melanocytosis. *Arch Ophthalmol* 1956; **56:** 830–2.

2 Gonder JR, Shields JA, Albert DM, Augsburger JJ, Lavin PT. Uveal malignant melanoma associated with ocular and oculodermal melanocytosis. *Ophthalmology* 1982; **89:** 953–60.

3 Lo C, Kiribuchi T, Maruo T. Malignant melanoma of the choroid associated with the nevus of Ota. In: Shimuzu K, Oosterhuis JA, eds. *Ophthalmology. International Congress Series 450.* Amsterdam: Excerpta Medica, 1979; **2:** 1959–62.

4 Dorrey CS, Montgomery H. Blue nevus and its distinction from Mongolian spot and the nevus of Ota. *J Invest Dermatol* 1954; **22:** 225–36.

5 Hulke JW. A series of cases of carcinoma of the eyeball. *R Lond Ophthalmic Hosp Rep* 1961; **3:** 279–86.

6 Albert DM, Scheie HG. Nevus of Ota with malignant melanoma of the choroid: report of a case. *Arch Ophthalmol* 1963; **69:** 774–7.

7 Yamamoto T. Malignant melanoma of the choroid in the nevus of Ota. *Ophthalmologica* 1969; **159:** 1–10.

8 Gondel JR, Shields JA, Albert DM. Malignant melanoma of the choroid associated with oculodermal melanocytosis. *Ophthalmology* 1981; **88:** 322–76.

9 Font RL, Reynolds AM Jr, Zimmerman LE. Diffuse malignant melanoma of the iris in the nevus of Ota. *Arch Ophthalmol* 1967; **77:** 513–8.

10 Jay B. Malignant melanoma of the orbit in a case of oculodermal melanosis (naevus of Ota). *Br J Ophthalmol* 1965; **49:** 359–63.

11 Hagler WS, Brown CC. Malignant melanoma of the orbit arising in a nevus of Ota. *Ophthalmology* 1966; **70:** 817–22.

12 Sang DN, Albert DM, Sober AJ, McMeekin TO. Nevus of Ota with contralateral cerebral melanoma. *Arch Ophthalmol* 1977; **95:** 1820–4.

13 Reese AB. Melanosis oculi: a case with microscopic findings. *Am J Ophthalmol* 1925; **8:** 865–70.

14 Yanoff M, Zimmerman LE. Histogenesis of malignant melanoma of the uvea III. The relationship of congenital ocular melanocytosis and neurofibromatosis to uveal melanomas. *Arch Ophthalmol* 1967; **77:** 331–6.

Accepted for publication 15 December 1986.

British Journal of Ophthalmology, 1988, 72, 134–138

Radiotherapy of periocular basal cell carcinomas: recurrence rates and treatment with special attention to the medical canthus

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SUMMARY Basal cell carcinomas of the eyelids, especially those in the medial canthal area, may cause extensive local destruction. Recurrent tumours are more aggressive and become progressively more difficult to treat; this is especially true for postirradiated recurrent, medial canthal, basal cell carcinomas. Tumours in this area should thus be treated by a technique which allows tissue sampling in order to gauge the adequacy of the treatment, with the goal being complete extirpation of the tumour. Excision monitored by frozen section control or Mohs' surgery is our recommendation based on a retrospective analyses of 631 eyelid basal cell carcinomas, half of which were primary tumours and half recurrent.

Of all malignant eyelid lesions 90% are basal cell carcinomas. The lower lids are the primary area of involvement in over 70% of cases, followed in relative frequency by the medial canthus, upper lid, and lateral canthus.[1] Characteristically, basal cell carcinomas are non-metastasising tumours which have, however, a great tendency to recur. Medial canthal lesions, which account for the second most common site of this tumour in its primary form, can spread deeply into the orbit and sinuses, eventually requiring exenteration for cure. A recurrence in this area can thus be especially devastating.

In treating eyelid tumours the considerations are many and varied. The usual principles of cancer surgery, to obtain an adequate margin of normal tissue about a malignancy, may partly give way to anxiety about cosmetic appearance and preservation of lacrimal and lid functions and their overall effects on the globe.

Periocular basal cell carcinomas are treated by a wide variety of methods and medical practitioners. Surgical excision, cryosurgery, currettage-electrodesiccation, radiotherapy, and Mohs' surgery all have their proponents and all are said to have five-year cure rates better than 90%.[2-5]

Many studies have shown that a lesion which has had prior treatment, regardless of what treatment, has a greater incidence of subsequent recurrence than a primary tumour.[6,7] The observation has been made by previous investigators that basal cell carcinomas which have received radiation therapy as their primary form of treatment recur at a higher rate and become more aggressive subsequently than tumours treated by different means.[8-11]

Because of our clinical impression that many recurrent medial canthal lesions we were treating had previously received radiation therapy, and because we found these tumours to be more aggressive and destructive, we decided to perform a retrospective study of eyelid basal cell carcinomas and to study the previously radiated lesions.

Materials and methods

A retrospective analysis of 631 consecutive cases of biopsy proved basal cell carcinomas of the eyelids was performed. Approximately half were primary lesions and half had been previously treated. Fifty five cases (59 lesions) were of recurrent tumours whose primary form of treatment had been radiation therapy. The majority of these patients had definitive treatment performed by Mohs' operation (PR),

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conventional surgery (BS), or a combination of these. The following parameters were examined: (1) patient's sex and age, (2) location of lesion, (3) time from previous therapy to recurrence, (4) recurrence rate after definitive surgery. The average follow-up time was 6·1 years. Neither the original size of the tumours (in recurrent cases) nor the methods, dosage, or exact techniques of radiation were available for comparison in all charts.

Results

Overall for the 631 lesions a five-year cure rate of 98·1% for primary tumours and 93·6% for recurrent tumours was achieved. See Tables 1 and 2.

In the group of 55 patients (59 lesions) that had received radiation therapy as the primary form of treatment there were 25 males with an average age of 63·3 years (range 35–85 years) and 30 females with an average age of 62·5 years (range 37–86 years). The average time from radiation therapy to recurrence was 5·3 years (range 6 months–20 years). The radiation dose given these patients averaged close to 4000 rads (range 1000–6000 rads) and treatment was fractionated over 6–29 sessions. Again, data on the exact specifics of radiation techniques were not available in all the charts.

The location of these postirradiated recurrent lesions was as follows: 42 medial canthus, 4 lateral canthus, 8 upper lid, 5 lower lid. After definitive surgery 7/59 lesions recurred again (11·9%); all seven were located in the medial canthus, and three of these patients have required exenteration. Medial canthal lesions were further studied. There were 243 tumours located at this site: 127 were primary, untreated tumours. In this group there have been six recurrences (4·7%). One hundred and sixteen lesions had received previous therapy. Eleven recurrences were seen in this group (9·5%). The group of 116 medial canthal basal cell carcinomas that had received some prior therapy was further analysed. Seventy four lesions in this group had been treated by methods other than radiation therapy, and four recurred (5·4%). In the 42 radiated medial canthal tumours there were seven recurrences (16·7%).

Table 1 *Basal cell carcinomas five years after definitive surgery*

Eyelids, all sites	*Recurrence rate*
Primary lesions (n=318)	1·9% (n=6)
Prior treatment (n=313)	6·4% (n=20)*

*p=0·008.

Table 2 *Basal cell carcinomas five years after definitive surgery*

Medial canthus (n=243)	*Recurrence rate*
Primary lesions (n=127)	4·7% (n=6)
Prior treatment (n=116)	9·5% (n=11)*
Prior treatment (n=116)	
No radiation (n=74)	5·4% (n=4)
Radiation (n=42)	16·7% (n=7)†

*p=0·22. †p=0·09.

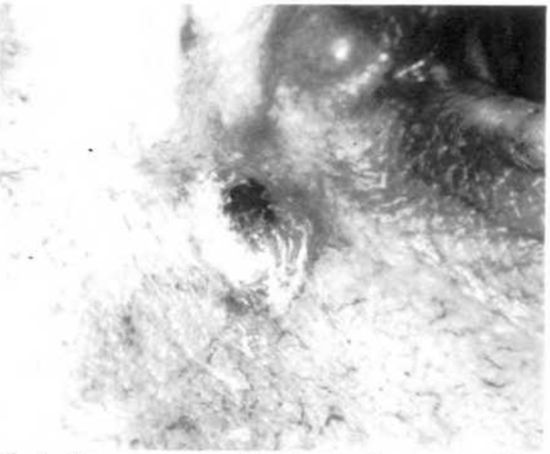

Fig. 1 *Recurrent postirradiated basal cell carcinoma of left lower lid-medial canthus area.*

The following cases are representative.

Case 1. Fig. 1 shows a recurrent previously irradiated basal cell carcinoma in the lower lid to medial canthus area.

Note the surrounding telangiectasis characteristic of a radiodermatitis. Fig. 2 shows the extent of surgery required to achieve a tumour free field. The

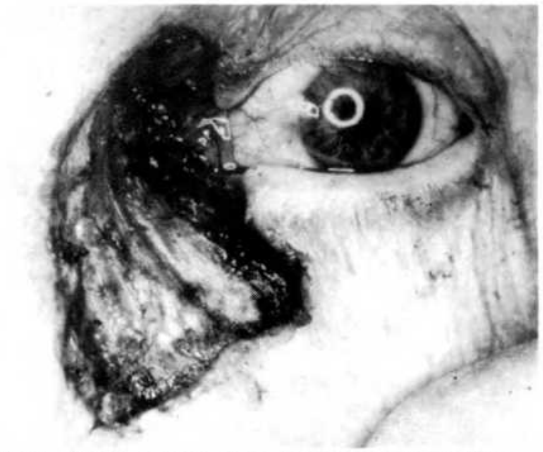

Fig. 2 *Resection required to achieve tumour-free field for patient in Fig. 1. The lacrimal system had to be sacrificed.*

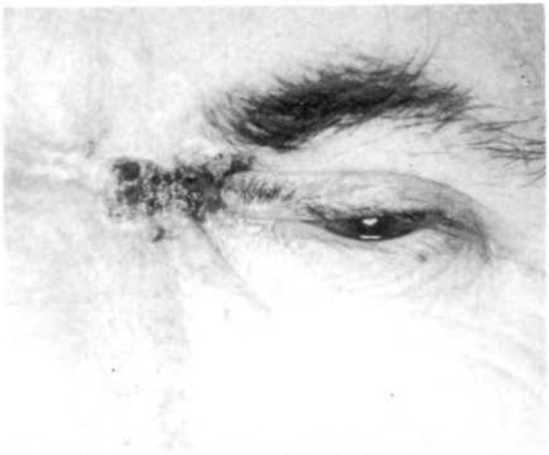

Fig. 3 *Recurrent postirradiated basal cell carcinoma of medial canthus. Tumour is fixed to and infiltrating bone.*

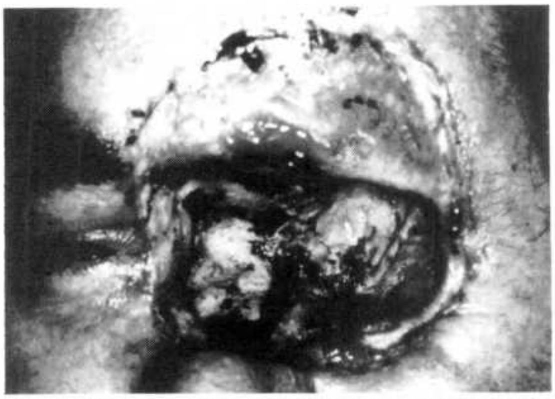

Fig. 4 *Extent of surgery required to get completely around tumour. The medial rectus muscle, conjunctiva, and bone were all infiltrated by cancer cells.*

lacrimal system had to be sacrificed but the globe was saved.

Case 2. Fig. 3 shows a recurrent postirradiated medial canthal basal cell carcinoma. This tumour is fixed to the underlying bone and distorts the canthal anatomy. To get to an area devoid of cancer cells not only was an exenteration required (the medial rectus and conjunctiva were also infiltrated with tumour) but part of the patient's nose and frontal bone had to be sacrificed (Fig. 4).

Discussion

The clinician has a much better chance of totally eradicating a tumour by treating it aggressively in its primary, virgin state. The chance for successful long term cure after recurrence is considerably less. Irrespective of the mode of treatment, recurrence rates for primary lesions range from 1 to 8%. Kopf and associates[12] in a study of curettage-electrodesiccation treatment of primary basal cell carcinomas found a 94% five-year cure rate but noted this was considerably less for head and neck (including eyelid) tumours. Eyelid basal cell carcinomas treated by radiation therapy are reported to have a 92–95% five-year cure rate.[13-15] These figures closely approximate the 94% cure rate achieved by Fraunfelder and associates[5] in their cryosurgical treatment of eyelid basal cell carcinomas. In this report one notes that lesions less than 10 mm in diameter had a 2% recurrence rate, while for tumours greater than 10 mm in diameter the recurrence rate increased to 9·5%. Concerning conventional surgery, Aurora and Blodi[10] found that 23% of cases had incomplete tumour excision. Gooding *et al.*[16] have shown that in cases of marginal extension of tumour one-third will recur. Chalfin and Putterman[2] have noted surgical recurrence rates ranging from 0 to 20%, reflecting what they believe to be differences in surgical technique. These authors recommend excision under frozen section control as the primary form of treatment. Doxanas *et al.*[17] reported that out of 126 cases of surgically excised tumours without frozen section monitoring of margins a recurrence rate of 5·5% was seen. For 39 other cases in which frozen section control was employed no recurrences were noted. Bart and his associates[18] found a 93·2% cure rate for 486 cases of primary basal cell carcinoma treated by surgical excision with primary closure. Concerning chemosurgery, Robins[19] has found a 98·2% five-year cure rate for primary basal cell carcinomas treated by this method.

For previously treated tumours the cure rate decreases and recurrences of up to 25% have been reported.[6 7 20] A 16% recurrence rate for previously treated eyelid basal cell carcinomas versus a 10% recurrence rate for primary tumours was reported by Payne *et al.*[21] Dizon and associates[22] reported on 12 patients with 20 recurrent eyelid basal cell carcinomas: eight of these 20 lesions were located in the medial canthus, which is about double the normal rate one would expect for primary medial canthal lesions. Menn *et al.*[7] studied 100 recurrent, retreated basal cell carcinomas and found that almost 50% recurred again following treatment. According to Kaplin and Zarem[23] 86% of all primary basal cell carcinomas occur on the face, but 94·5% of all recurrent lesions are found there, especially in the nasal and periorbital areas. Mora and Robins[24] in a study of 848 cases of basal cell carcinoma found that location at the centre of the face, including eyelids, accounted for over one-third of the total number seen and that these tumours were more invasive, more destructive, and more difficult to treat than those at other sites.

Concerning medial canthal lesions, McGregor[25] in a study of 88 basal cell carcinomas of the inner canthus treated by cold steel surgery found a recurrence rate of 3·6%. Aurora and Blodi[10] found that extensive basal cell carcinomas were 1·5 times more frequent in the inner canthus and that radiotherapy as compared with excision gave a higher recurrence rate. Cobett[26] reported a 20·5% re-recurrence rate after surgical excision for primarily irradiated lesions. Abraham and co-workers[27] noted a 10% recurrence rate for radiated medial canthal basal cell carcinomas versus a 7·4% recurrence for surgically treated tumours. Taylor and Barisoni[11] also found a lower recurrence rate for surgically excised basal cell tumours as opposed to those treated by other methods, including radiation, in which a 17% recurrence rate was found. The periorbital region was found to be the area with the highest recurrence rate by these investigators.

The medial canthus is an area of complex anatomy which requires thorough familiarity and skill in order to perform adequately the required tumour debulking and reconstructive procedure. Clinicians not so versed in these operations might shy away from treating cancers in this area and refer the patients for radiotherapy, which they might regard as allowing for better cosmetic results. This may explain why the majority (42/59=71·2%) of the radiated lesions were medial canthal. Perhaps also the medial canthal tumours were the larger ones, further instilling fear in the prospective surgeon. If this latter point were true, then a size difference alone can perhaps account in part for a higher recurrence for medial canthal lesions.

The possible reasons why tumours recur are essentially three: (1) inadequate therapy, with part of the tumour being left behind; (2) multicentricity of origin, with new crops of tumour cells at different areas; and (3) the therapy given induced new tumour formation. All these factors have to be considered, but for radiation therapy the last is the more likely possibility as compared with the other treatments. Hirshowitz and Mahler[8] postulate a tumour-host relationship which may be weakened by radiotherapy, thereby breaking down barriers to tumour spread. Ceilley and Anderson[28] believe that any previous therapy, but especially radiotherapy, may disturb the protective barrier offered by the periosteum and allow for bony cancerous involvement. Perhaps also radiation effects on the skin cause fibrotic changes and irregular dermal planes which allow easier egress for tumour micrometastases.

CONCLUSION

The data we have presented, though not statistically significant, are certainly suggestive of a trend. We believe they support the view that recurrent lesions are more aggressive and have a higher re-recurrence rate than primary lesions, and that previously irradiated tumours recur at a higher rate than lesions treated by other methods.

As noted previously, we do not have the original sizes of the tumours nor the exact techniques of radiation for all patients studied; these factors can obviously influence the results. We therefore do not want wholeheartedly to condemn radiation therapy, but do consider that medial canthal basal cell carcinomas, because of their higher recurrence rate and greater propensity to invade the orbit, should be treated in such a way that tissue can be sampled to assure adequacy of therapy, such as by Mohs's operation or excision monitored by frozen section control.

Dr Rodriguez-Sains was supported by a fellowship grant from the Heed Ophthalmic Foundation.

References

1 Henkind P, Friedman A. Cancer of the lids and ocular adnexa. In: Andrade R, Gumport S, Popkin G, Rees TD, eds. *Cancer of the skin*. Philadelphia: Saunders, 1976: 1345–71.
2 Chalfin J, Putterman AM. Frozen section control in the surgery of basal cell carcinoma of the eyelid. *Am J Ophthalmol* 1979; **87**: 802–9.
3 Robins P. Mohs' chemosurgery for tumors in the periorbital area. In: Jakobiec FA, ed. *Ocular and adnexal tumors*. Birmingham: Aesculapius, 1978: 525–31.
4 Gladstein AH. Radiotherapy of eyelid tumors. In: Jakobiec FA, ed. *Ocular and Adnexal Tumors*. Birmingham: Aesculapius, 1978: 508–16.
5 Fraunfelder FT, Zacarian SA, Limber BL, Winefield D. Cryosurgery for malignancies of the eyelid. *Ophthalmology* 1980; **87**: 461–5.
6 Hayes H. Basal cell carcinoma: the East Grinsted experience. *Plast Reconstr Surg* 1960; **30**: 273–9.
7 Menn H, Robins P, Kopf AW, Bart RS. The recurrent basal cell epithelioma: a study of 100 cases of recurrent, retreated basal cell epitheliomas. *Arch Dermatol* 1971; **103**: 628–31.
8 Hirshowitz B, Mahler D. Incurable recurrences of basal cell carcinoma of the mid-face following radiation therapy. *Br J Plast Surg* 1971; **24**: 205–11.
9 Hirshowitz B, Mahler D. Unusual case of multiple basal cell carcinomas with metastases to the parotid lymph gland. *Cancer* 1968; **22**: 654–7.
10 Aurora AL, Blodi FC. Reappraisal of basal cell carcinoma of the eyelids. *Am J Ophthalmol* 1970; **70**: 329–36.
11 Taylor GA, Barisoni D. Ten years experience in the surgical treatment of basal cell carcinoma; a study of factors associated with recurrence. *Br J Surg* 1973; **60**: 522–5.
12 Kopf AW, Bart RS, Schraeger D, Lazar M, Popkin GL. Curettage and electrodesiccation treatment of basal cell carcinoma. *Arch Dermatol* 1977; **113**: 439–43.
13 Fitzpatrick PJ, Jamieson DM, Thompson GA, Allt WEC. Tumors of the eyelids and their treatment by radiotherapy. *Radiology* 1972; **104**: 661–5.
14 Bart RS, Kopf AW, Petratos MA. *X*-ray therapy of skin cancer:

evaluation of a 'standardized' method of treating basal cell epitheliomas. *Proceedings of the American Cancer Society*. Philadelphia: Lippincott, 1970: 559–70.

15 Gladstein AH. Efficacy simplicity and safety of *x*-ray therapy of basal cell carcinomas on periocular skin. *J Dermatol Surg Oncol* 1978; **4:** 586–93.

16 Gooding CA, White G, Yatsuhashi M. Significance of marginal extension of excised basal cell carcinoma. *N Engl J Med* 1965; **273:** 923–4.

17 Doxanas MT, Green WR, Iliff CE. Factors in the successful management of basal cell carcinomas of the eyelids. *Am J Ophthalmol* 1981; **91:** 726–36.

18 Bart RS, Schraeger D, Kopf AW, Bromberg J, Dubin W. Scalpel excision of basal cell carcinoma. *Arch Dermatol* 1978; **114:** 739–42.

19 Robins P. Chemosurgery, my 15 years experience. *J Dermatol Surg Oncol* 1981; **7:** 779–89.

20 Rank BK, Wakefield AF. Surgery of basal cell carcinomas. *Br J Surg* 1959; **45:** 531–3.

21 Payne JW, Duke JR, Butner RB, Eifrig DE. Basal cell carcinoma of the eyelids: a long term follow-up study. *Arch Ophthalmol* 1969; **81:** 553–8.

22 Dizon RV, Shannon GM, Siliguini JJ. Basal cell carcinoma recurrence: early diagnosis and surgical treatment. *Ophthalmic Surg* 1977; **8:** 31–9.

23 Kaplin L, Zarem H. Recurrent basal cell carcinoma; a review concerning the incidence, behavior, and management of recurrence basal cell carcinoma with emphasis on the incompletely excised lesion. *Plast Reconst Surg* 1980; **65:** 656–64.

24 Mora R, Robins P. Basal cell carcinomas in the center of the face. Special diagnostic, prognostic, and therapeutic considerations. *J Dermatol Surg Oncol* 1978; **4:** 315–21.

25 McGregor JC. A study of basal cell carcinoma of the inner canthus 1967–72. *Br J Surg* 1979; **66:** 522–3.

26 Cobbett JR. Recurrence of rodent ulcers after radiotherapy. *Br J Surg* 1965; **52:** 347–9.

27 Abraham JC, Jabaley ME, Hoopes JE. Basal cell carcinoma of the medial canthal region. *Am J Surg* 1973; **126:** 492–5.

28 Ceilley RI, Anderson RL. Microscopically controlled excision of malignant neoplasms on and around eyelids followed by immediate surgical reconstruction. *J Dermatol Surg Oncol* 1978; **4:** 52–62.

Accepted for publication 15 December 1986.

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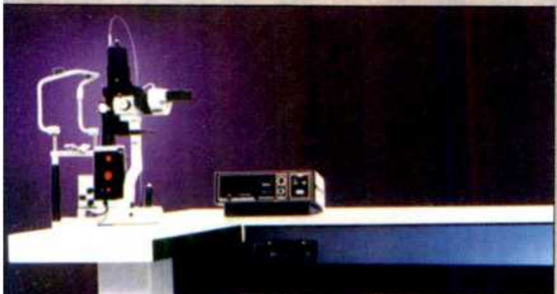

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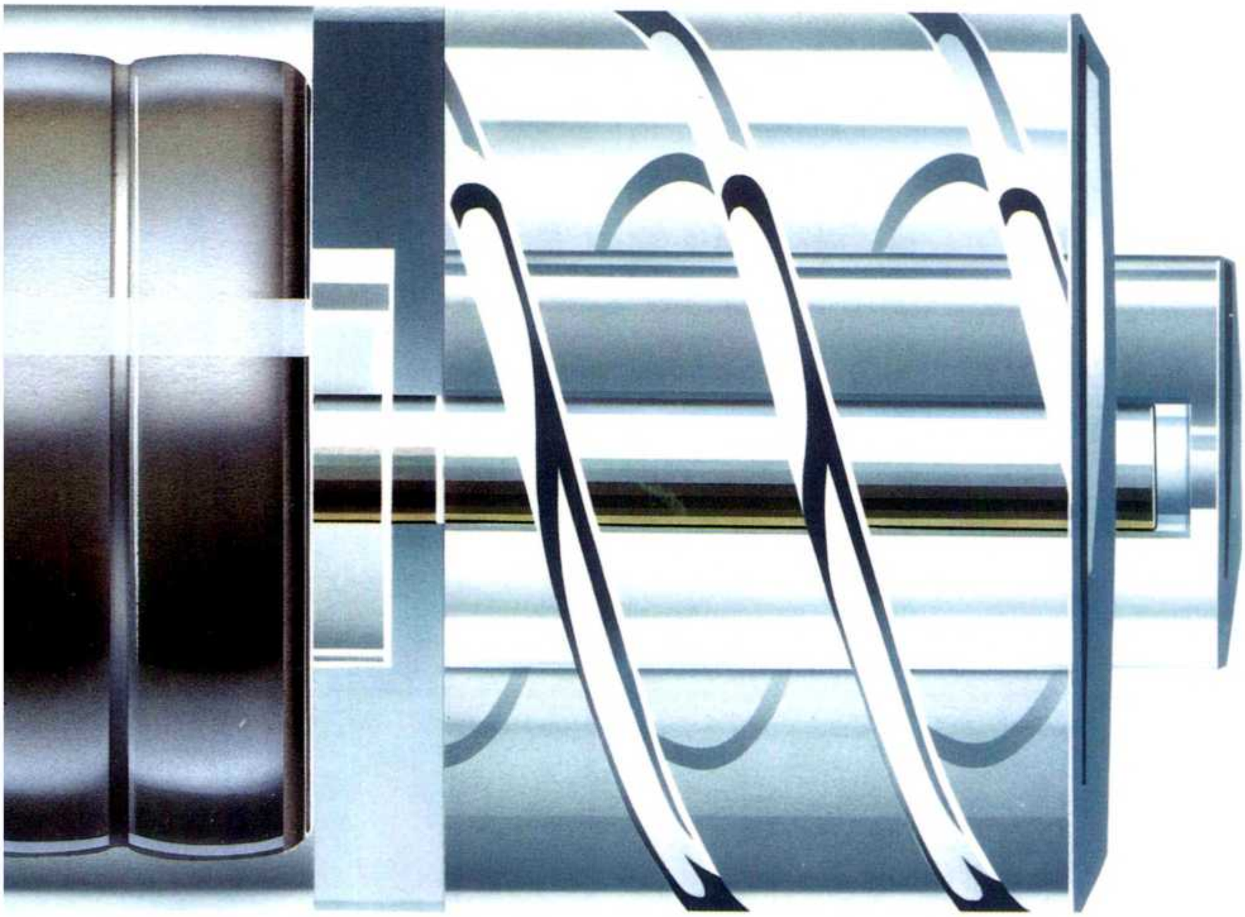

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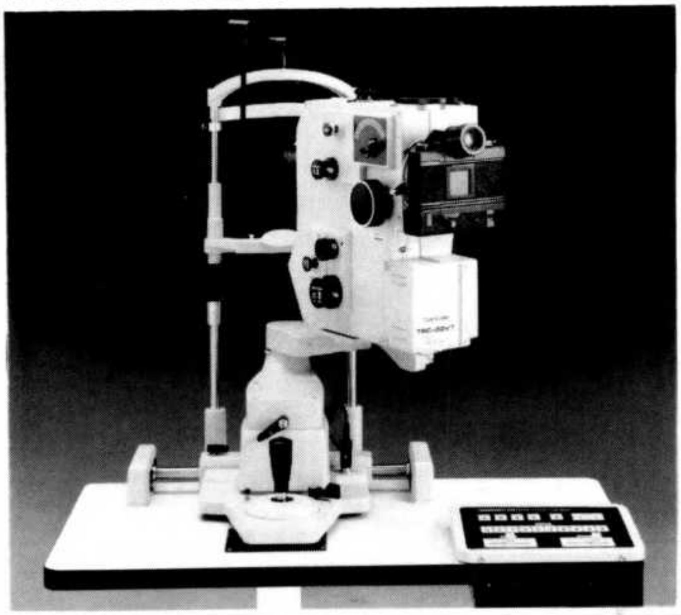

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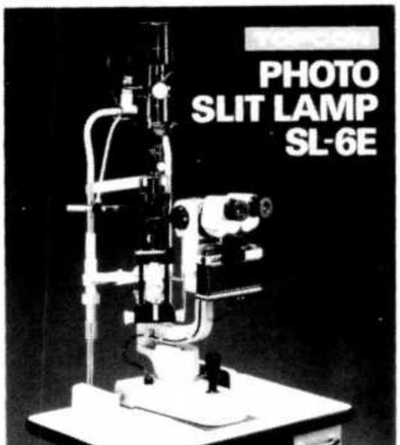

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British Journal of Ophthalmology, 1988, **72**, 139–141

Neurofibromatosis associated with retinoblastoma: case report

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SUMMARY A case of neurofibromatosis is presented in a 3-year-old male with leucokoria in his left eye. Enucleation was performed, and on pathological examination the mass filling the globe proved to be retinoblastoma. We believe ours to be the first reported case of this rare association.

Neurofibromatosis is an irregularly transmitted autosomal dominant, neurocutaneous, hereditary disorder that has incomplete penetrance and variable expressivity. It results from dysplasia of neuroectodermal and mesodermal tissues. Glial and melanocytic hamartomas of the retina and uveal tract can be found in patients with this disease.

Our case is a rare association of neurofibromatosis and retinoblastoma—a malignant tumour of neuroectodermal origin—in a 3-year-old male. It is among the retinal tumours reported in association with neurofibromatosis.

Case report

A 3-year-old boy was seen in our outpatient department on 20 February 1986 because of leucokoria in his left eye (Fig. 1). His parents had been aware of

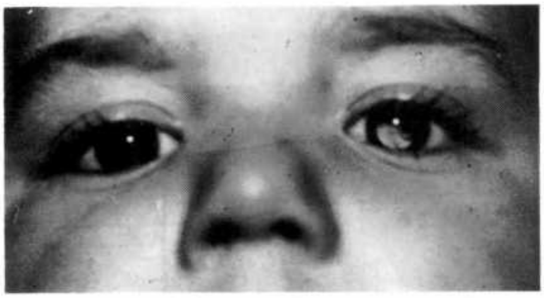

Fig. 1 *Leucokoria in the left eye.*

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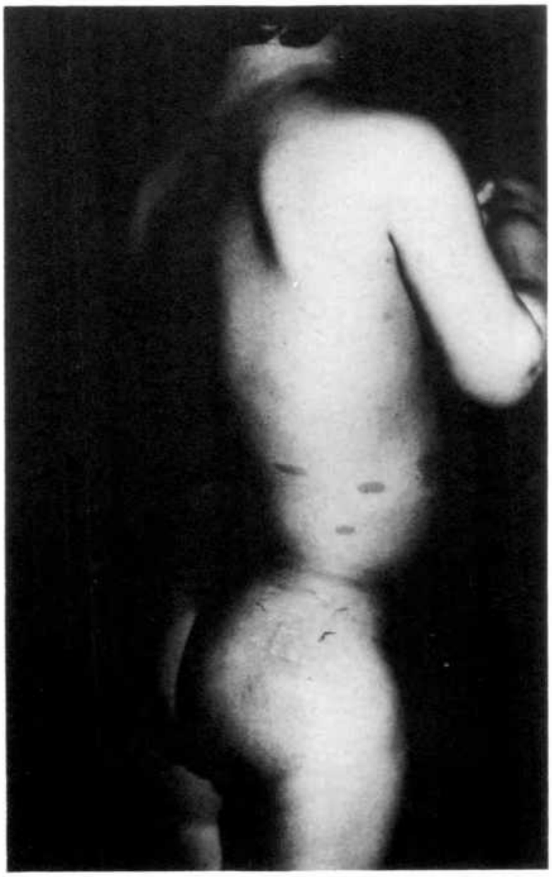

Fig. 2 *Café-au-lait spots on the body.*

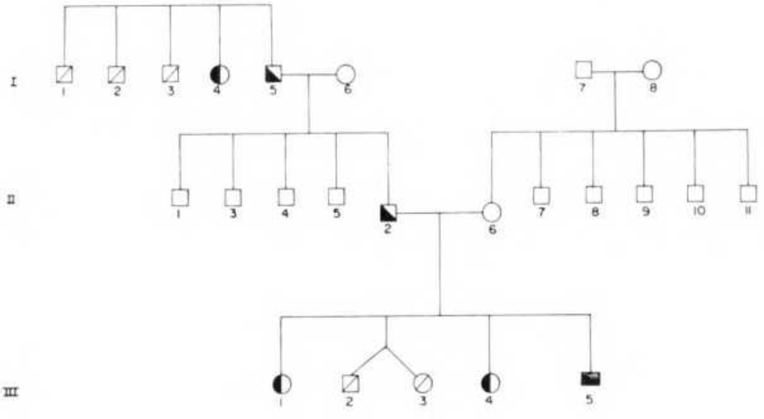

Fig. 3 *The family tree.* □ *Male.* ○ *Female.* ◪ *Male with neurofibromatosis.* ◐ *Female with neurofibromatosis.* ■ *Proband with neurofibromatosis and retinoblastoma.* /=*died.*

this white pupillary sign for about 1·5 months, but they did not consider it important.

On systemic examination he had large and small café-au-lai spots over the trunk and upper right arm of his body (Fig. 2), and there was a family history of neurofibromatosis (Fig. 3).

Examination of the left eye disclosed a pinkish white mass without pigmentation filling the entire globe, clinically suggesting retinoblastoma. The retina was detached and could be seen in the pupillary area. The visual acuity could not be measured. The cornea and lens were clear. Radiographic examination did not show any calcification. A and B mode ultrasonographic examination supported the diagnosis, showing a solid mass behind the lens. Chromosomal analysis revealed a normal karyotype.

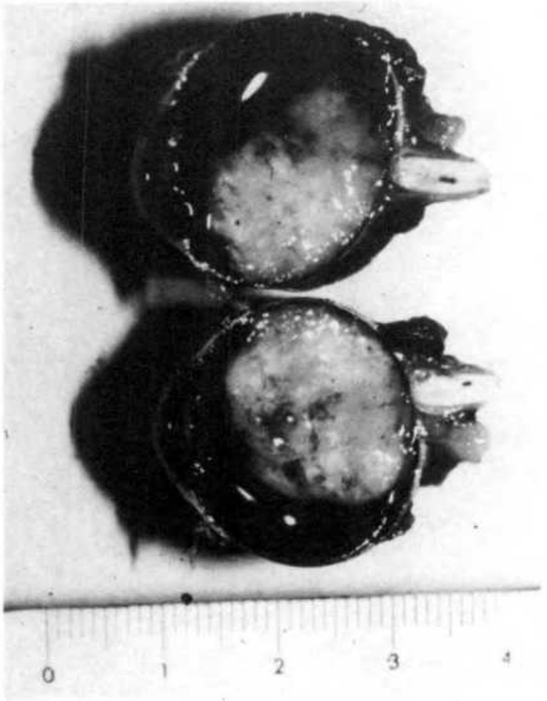

Fig. 4 *Gross specimen of retinoblastoma.*

Enucleation was performed, and the bulbus with 10 mm of optic nerve behind the globe was removed eight days later under general anaesthesia. Examination of the fundus of the other eye showed no abnormality.

The left bulbus was of normal size, and a tumour continuing with the retina grew towards vitreous, which showed large areas of necrosis (Fig. 4). Histopathologically, the cells that form the neoplasm had large hyperchromatic nuclei with minimal amounts of cytoplasm. In some areas these cells were attached to each other, forming rosettes (Fig. 5). The final diagnosis was retinoblastoma. The optic disc was found to be intact.

Discussion

Neurofibromatosis and retinoblastoma are both considered to be predisposing conditions to second malignant neoplasms. In neurofibromatosis, dysplasia, hyperplasia, and neoplasia of a variety of tissues are encountered, and the gene for this disease could be regarded as an example of a cancer gene.[1] Three factors highly suggestive of the malignant potential of the disease are unusual tumours, multiple tumours, and young age at diagnosis.[2] The tumours in neurofibromatosis are generally derived from Schwann cells of peripheral and cranial nerves, and glial cells of the central nervous system. Malignant neural and more rarely melanocytic tumours occur in approximately 0·3% of the patients.[3-6]

Our case presents an association of retinoblastoma,

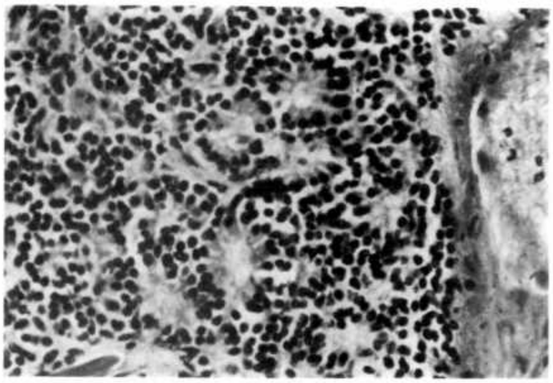

Fig. 5 *Histopathological section of the tumour. Flexner-Wintersteiner rosettes are visible. Haematoxylin and eosin.*

a tumour of neuroectodermal origin,[7] with neurofibromatosis. Although this may be a chance association, it is not surprising, since tumours of neural crest and non-neural crest origin have been reported to occur in neurofibromatosis, and the disease is considered to be a predisposing cause of second malignant neoplasms.

Schwannoma, neurilemmoma, acoustic neuroma, optic glioma, meningioma, ganglioneuroma, naevus of Ota, and choroidal melanoma, all tumours of neural crest derivatives—that is, Schwann cells, glial cells, and melanocytes—have been reported in association with neurofibromatosis.[8,9] Wilms' tumour, acute leukaemia, rhabdomyosarcoma, neuroblastoma, and malignant fibrous histiocytoma are other non-neural crest malignancies reported in cases of neurofibromatosis.[1,2]

It has also been reported that second tumours may follow radiation treatment or chemotherapy, or be unassociated with radiation therapy, mostly in patients with bilateral retinoblastomas. The reported tumours are bone sarcoma, soft tissue sarcoma, leukaemia, lymphoma, brain tumour, skin carcinoma, melanoma, histiocytosis X. Those that cannot be related to radiation therapy imply a common chromosomal origin with retinoblastoma.[10]

Our case was a unilateral retinoblastoma with no family history and normal chromosomal findings. It is known that certain unilateral sporadic cases of retinoblastoma are germinal mutations, and 10%–15% of these patients transmit the disease to their offspring.[11] If this is so with our case, it leads us to believe that the genetic abnormality leading to neurofibromatosis played some part in the development of the retinal tumour.

A retinal tumour in neurofibromatosis is likely to be an astrocytoma, though this is less frequently seen in neurofibromatosis than in tuberous sclerosis.[12] Consequently we recommend that a retinal tumour in neurofibromatosis should be examined and followed up carefully, because if it is a retinoblastoma it can be cured by methods other than enucleation if diagnosed early.

References

1 Wertelecki W, Iinuma K, Bentley HP. Non-neural malignancy complicating neurofibromatosis in two relatives. *Cancer Genet Cytogenet* 1985; **18:** 87–9.
2 Warrier RP, Kini KR, Raju U, Shumacher B, Wu K. Neurofibromatosis and malignancy. *Clin Pediatr* 1985; **24:** 584–5.
3 Brownstein S, Little JM. Ocular neurofibromatosis. *Ophthalmology* 1983; **91:** 1595–9.
4 Font RL, Ferry AP. The phakomatoses. *Int Ophthalmol Clin* 1972; **12:** 1–5.
5 Yanoff M, Fine BS. *Ocular pathology. A text and atlas.* 2nd ed. Philadelphia: Harper and Row, 1982: 33–9.
6 Wiznia RA, Freedman JK, Mancini AD, Shields JA. Malignant melanoma of the choroid in neurofibromatosis. *Am J Ophthalmol* 1978; **86:** 684–7.
7 Russel DS, Rubinstein LJ. *Pathology of tumors of the nervous system.* 4th ed. Edinburgh: Constable, 1977: 48–55, 299–307.
8 Croxatto JO, Charles DE, Malbran ES., Neurofibromatosis associated with nevus of Ota and choroidal melanoma. *Am J Ophthalmol* 1981; **92:** 578–80.
9 Hope DG, Mulvihill JJ. Malignancy in neurofibromatosis. In: Richard VM, Mulvihill JJ, eds. *Advances in neurology.* New York: Raven Press, 1981: 33–56.
10 Meadows AT, Baum E, Fossati-Bellani F, *et al.* Second malignant neoplasms in children. An update from the late effects study group. *J Clin Oncol* 1985; **3:** 532–8.
11 Ellsworth RM. Retinoblastoma. In: Duane TD, ed. *Clinical ophthalmology.* Philadelphia: Harper and Row, 1985: **3:** chapter 35: 2.
12 Ulbright TM, Fulling KH, Helveston EM. Astrocytic tumors of the retina. *Arch Pathol Lab Med* 1984; **108:** 160–3.

Accepted for publication 4 December 1986.

British Journal of Ophthalmology, 1988, **72,** 142–144

Acute angle closure glaucoma precipitated by orbital pseudotumour

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SUMMARY A 62-year-old woman presented with acute angle closure glaucoma. After a poor response to conventional treatment the presenting signs were re-evaluated and a diagnosis of pseudotumour of the orbit was made. Treatment with oral steroids resolved both the glaucoma and the orbital pseudotumour. The presumed pathogenesis and literature are reviewed.

A secondary rise in intraocular pressure may have both ocular and orbital causes. Open angle glaucoma secondary to elevated episcleral venous pressure may result from orbital processes such as thyroid disease, pseudotumour, arterovenous malformation, and varices.[1] Secondary angle closure glaucoma can follow central retinal vein occlusion,[2] buckling procedures[3] with reactive lymphoid hyperplasia,[4] posterior scleritis,[5] and in association with acquired immune deficiency syndrome (AIDS).[6] We describe here a case of orbital pseudotumour that presented with acute angle closure glaucoma. Both the pseudotumour and the glaucoma resolved with systemic steroid treatment.

Case history

A 62-year-old white woman presented with a one-week history of right periorbital pain. There was no previous ocular history. She had a past history of gastric ulcer.

On admission her visual acuity was 6/12 (20/40) in the right eye and 6/9 (20/30) in the left. Examination of the right eye revealed a soft swollen upper eyelid with full extraocular movements. Slit-lamp examination showed moderate chemosis and conjunctival injection. The cornea was clear. The anterior chamber depth was 2·0 mm with no flare or cells. The lens and vitreous were clear. Applanation tonometry revealed an intraocular pressure of 35 mmHg; gonioscopy showed a closed angle for 270° and a slit angle in the lower quadrant. The pupil measured 4 mm in the dark and reacted sluggishly to light. Funduscopy showed a normal disc with 0·2 cup. The macula, blood vessels, and periphery were normal. In the left eye the eyelids were normal, a slit-lamp examination gave normal results, and the intraocular pressure was 14 mmHg. The anterior chamber depth was 2·2 mm

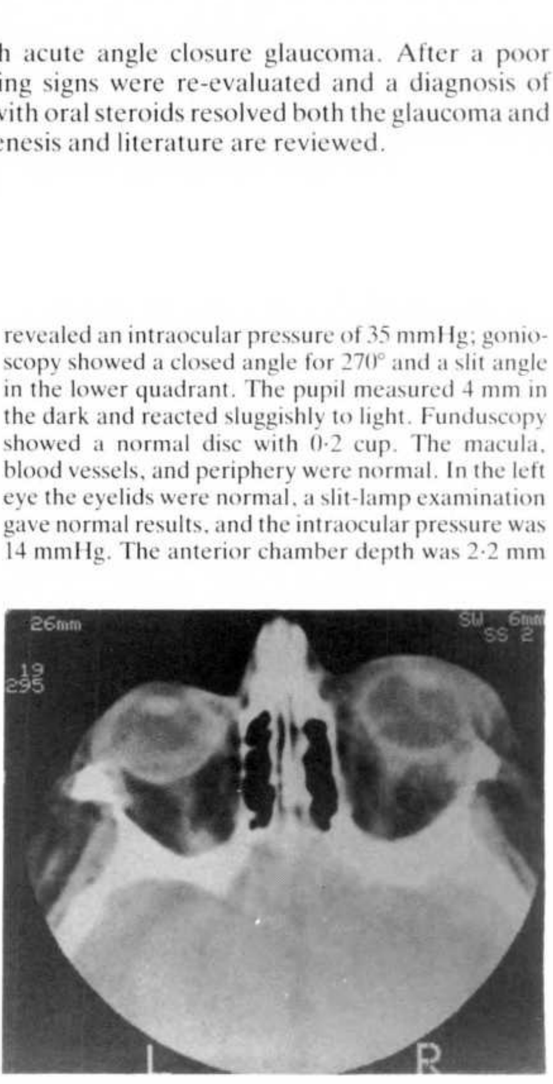

Fig. 1 *Axial CT scan without contrast demonstrates right exophthalmos with lid swelling, thickened sclera in the posterior aspect of the right globe, and retrobulbar tissue swelling.*

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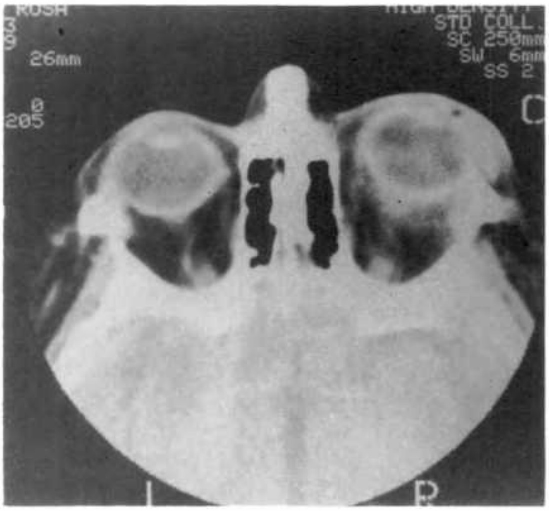


Fig. 2A *Axial CT scan with contrast demonstrates right scleral enhancement.*

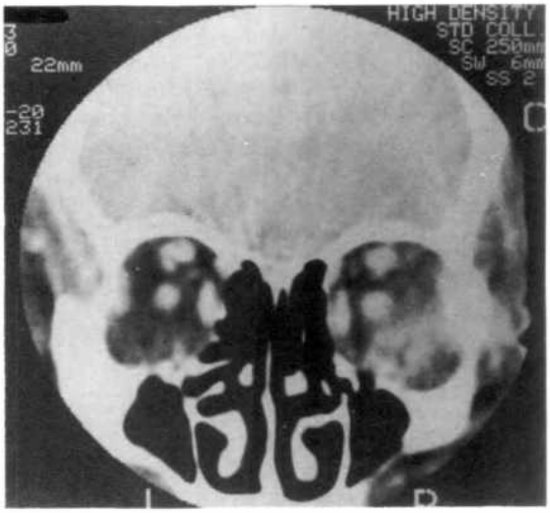


Fig. 2B *Coronal CT scan with contrast enhancement demonstrates swelling of retrobulbar soft tissue in the right orbit.*

and the angle was open to grade 3 for 360° with a slightly narrow entrance.

A trial of pilocarpine, acetazolamide, and glycerol lowered the pressure only transiently, and over the next 24 hours her condition deteriorated. Right exophthalmos of 4·5 mm developed, the chemosis became severe, and the extraocular movement became markedly restricted. There was resistance to retropulsion of the globe, but no mass was palpated. The anterior chamber shallowed to 1·6 mm, and fundus examination revealed a few choroidal folds near the macula.

The erythrocyte sedimentation rate (ESR) was 103 mm/h and the leucocytes 13×10^9 l (90% polymorphonuclear). The blood sugar was mildly raised at 172 mg/100 ml (9·5 mmol/l). Other laboratory data including thyroxin levels were normal. CT scanning done on the same day showed thickened sclera and enhanced retrobulbar soft tissue on the right side (Figs. 1, 2). The left side was normal.

The patient was started on 60 mg prednisone orally with cimetidine. Within six hours there was a dramatic clinical improvement. The pain, swelling, and chemosis decreased markedly. The extraocular movements became normal. The anterior chamber deepened to 2·1 mm, the intraocular pressure dropped to 15 mm, and the angle opened to grade III for 270°; the nasal quadrant was sealed by peripheral anterior synechiae.

On discharge from hospital her visual acuity in the right eye was 6/9+ (20/30+) and intraocular pressure was 15 mmHg. There was no exophthalmos, chemosis, or restricted ocular movements. The steroid dose was gradually tapered. The patient has remained asymptomatic for 18 months. Repeated CT scans showed a normal globe and orbit (Fig. 3).

Discussion

Orbital pseudotumour can affect men and women at any age, though middle age is most usual. Pain and proptosis are the commonest features. Glaucoma occasionally occurs and is usually caused by raised episcleral venous pressure. The diagnosis of pseudotumour of the orbit can be reliably confirmed by CT scan, and the response to steroids is usually prompt.

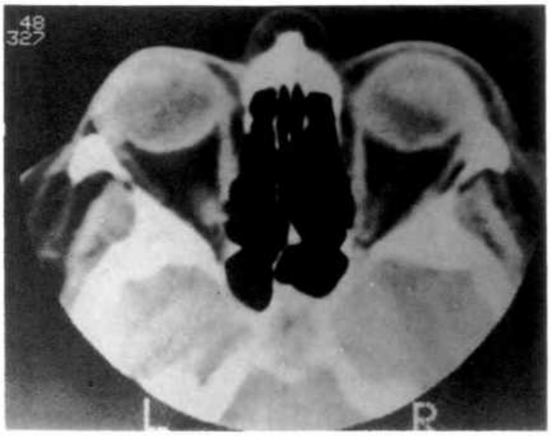


Fig. 3 *Axial CT scan without contrast. All pathological features disappeared.*

Uveal pseudotumour or reactive lymphoid hyperplasia without orbital involvement has been described.[4][7] In the case described by Gass[4] angle closure developed, and engorged ciliary processes were visible through the pupil. Similarly Quinlan and Hitchings[5] described three cases of angle closure glaucoma with posterior scleritis and choroidal effusions. Their cases responded to treatment with systemic oxyphenbutazone and cyclopentolate drops. In the present case ciliary processes were not observed, and the fundus was fairly normal. Harris and Rice[8] described a woman with a cavernous sinus carotid fistula who developed angle closure glaucoma. The glaucoma responded to conventional therapy. They suggested that generalised orbital venous engorgement caused uveal engorgement and compression of the anterior segment.

We believe the present case to be the first description of orbital pseudotumour precipitating angle closure glaucoma. The pathogenesis was probably similar to the case of Harris and Rice—that is, orbital congestion causing relative obstruction of the vortex veins. The swelling of the uvea pushed the iris-lens diaphragm forward, shallowing the chamber and closing the angle. Unlike the case of Harris and Rice our patient did not respond to pilocarpine but rather to treatment of the underlying condition (pseudotumour) with steroids. Pilocarpine may have further exacerbated the situation by inducing forward movement of the ciliary body. In contrast, cyclopentolate drops might have been useful until the improvement of the orbital congestion by the steroids.

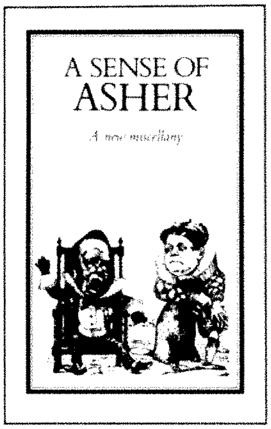
In our patient the contralateral eye had a slightly narrow entrance to the angle recess. We can assume that the affected eye had a similar appearance before the onset of the pseudotumour. In the normal course of events such an eye may have been only at moderate risk for developing angle closure. However, given the additional stimulus of a pseudotumour and presumed uveal swelling, frank angle closure developed.

Other cases of secondary angle closure in orbital pseudotumour may have gone unrecognised in the past because of the difficulty of measuring the intraocular pressure and performing gonioscopy in the presence of severe chemosis. Signs of orbital pseudotumour in cases of angle closure glaucoma may necessitate steroid treatment as an adjunct to or instead of breaking the attack by conventional means.

References

1 Yablonski ME, Podos SM. Glaucoma secondary to elevated episcleral venous pressure. In: Ritch R, Shields MB, eds. *The secondary glaucomas.* St Louis: Mosby, 1982: 207–17.
2 Hyams SW, Neumann E. Transient angle-closure glaucoma after retinal vein occlusion. Report of two cases. *Br J Ophthalmol* 1972; **56:** 353–5.
3 Phelps CD. Glaucoma associated with retinal disorders. In: Ritch R, Shields MB, eds. *The secondary glaucomas.* St Louis: Mosby, 1982: 153–6.
4 Gass JP. Retinal detachment and narrow angle glaucoma secondary to inflammatory pseudotumor of the uveal tract. *Am J Ophthalmol* 1967; **64:** 612–21.
5 Quinlan MP, Hitchings RA. Angle-closure glaucoma secondary to posterior scleritis. *Br J Ophthalmol* 1978; **62:** 330–5.
6 Ullman S, Wilson RP, Schwartz L. Bilateral angle closure glaucoma in association with the acquired immune deficiency syndrome. *Am J Ophthalmol* 1986; **101:** 419–24.
7 Ryan SJ, Frank RN, Green WR. Bilateral inflammatory pseudomotor of the ciliary body. *Am J Ophthalmol* 1971; **72:** 586–91.
8 Harris GJ, Rice PR. Angle closure glaucoma in carotid cavernous fistula. *Ophthalmology* 1979; **86:** 1521–9.

Accepted for publication 4 December 1986.



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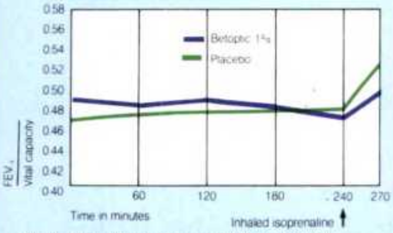
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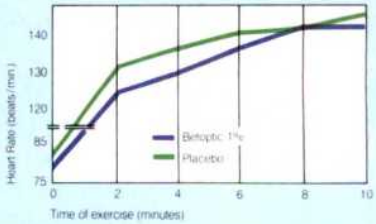
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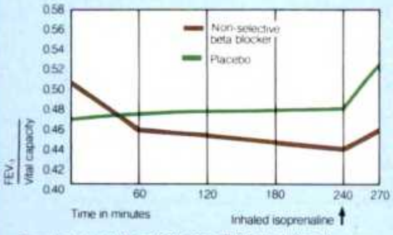
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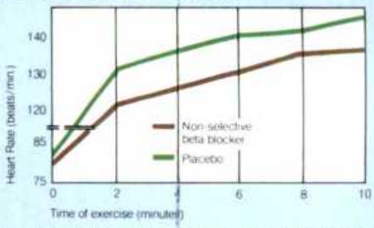
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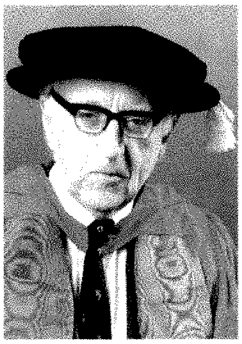

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British Journal of Ophthalmology, 1988, **72**, 145–149

Changes in astigmatism between the ages of 1 and 4 years: a longitudinal study

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SUMMARY Changes in astigmatism during development were studied in 299 infants with astigmatism as they grew from 1 to 4 years of age. All consecutive cases of 1-year-old infants with an astigmatism of 1·0 D or more in at least one eye found at an ophthalmic screening survey were selected for follow-up. The cycloplegic refraction was longitudinally followed at yearly intervals. During development there was no decrease in the degree of hypermetropia, but there was a significant decrease in the incidence and amount of astigmatism during the test period. The most pronounced decrease in magnitude and incidence of astigmatism occurred between the first and second year of life. The majority of astigmatic eyes of the 1-year-old infants had a horizontal curvature greater than the vertical (plus cylinder axis of 180°), and no changes of the axis of the astigmatism were noted during the following years.

Recent studies have shown that the incidence of astigmatism differs between infants and schoolchildren.[1 2] The high incidence of astigmatism in infancy and the much lower incidence in schoolchildren implies that much of the early astigmatism must be eliminated between the age of 1 and 6 years. Knowledge of the changes in astigmatism that take place during this period is required in order to understand the connection between astigmatism, spherical refraction, squint, and amblyopia.

The aim of this longitudinal study was to follow a population sample of astigmatic infants during a period of four years in order to evaluate the developmental changes of their astigmatism. It is now well documented by both retinoscopy[1-3] and photorefraction[4 5] that infants show a high percentage of astigmatism during the first year of life. Most of the astigmatism cases found during the first year of life have a plus cylinder axis of 180°. Schoolchildren at 6 years of age have a much lower incidence of astigmatism and almost exclusively a plus cylinder axis of 90°.[6] Atkinson *et al.*[7] reported that the incidence of astigmatism has declined to the level of the schoolchildren at the age of 18 months, while Mohindra and Held[8] reported a high incidence as late as 5 years of age.

In the present study we found that the number of cases with astigmatism and also the magnitude of the astigmatism decreased between 1 and 2 years of age. This was especially marked in those patients who lost all astigmatism at the age of 4. Furthermore, we found no change in the axis of astigmatism in any case from the age of 1 to 4 years.

Materials and methods

All parents in the city of Västerås (population 110 000) in Sweden are given information at the Children's Health Care Centre of a voluntary ophthalmic screening when the child is about 1 year of age. The ophthalmological control consists of an assessment of motility and alignment as well as cycloplegic retinoscopy. Nearly 50% of the children born in the city take part in the ophthalmic screening.

During a three-year period approximately 2200 infants were examined. Patients with an astigmatism of 1 D or more and without strabismus or ocular disease were selected for analysis and follow-up. Some of the children were lost in the yearly follow-up and were excluded from the study. Thus 299 cases with an astigmatism of 1 D or more in at least one eye remained through the whole study.

All refractions were written with a plus cylinder convention. The vertical curvature of the eye was considered greater than the curvature of the horizontal meridian if the plus cylinder axis was 90±15°

Correspondence to Maths Abrahamsson, Department of Ophthalmology, Sahlgren's Hospital, S-413 45 Göteborg, Sweden.

(with-the-rule astigmatism), and smaller if the axis was 180±15°. The spherical equivalent was defined as the algebraic sum of the spherical power of the lens system and half the power of the cylinder.

The children were refracted by a Heyne retinoscope 30 minutes after instillation of cyclopentolate (1%) by Lindner's method[9] of cylindersciascopy. The refraction procedure was repeated once a year and the follow-up period was four years.

Spectacles were prescribed for part-time use if the children had an astigmatism >1·0 D or ametropia >3 D at the age of 3 years. The cylindrical refraction was then corrected. Spectacles were prescribed for full-time use if any of the refractions showed an anisometropia ≥1·0 D. The anisometropia was then fully corrected.

Results

The astigmatic children were refracted on four occasions with an interval of one year, and the majority of cases showed a compound hyperopic astigmatism. Ten cases were myopic in both the horizontal and vertical meridian. The refraction values, represented by the spherical equivalent, are presented in Fig. 1. The distribution is bell-shaped with a maximum around +1·0 D. The spread of the curve decreased slightly between the age of 1 and 2 years and then remained constant. There was no decrease in hypermetropia, that is, there was no evidence for an age induced peak shift of the distribution.

Fig. 2A shows the astigmatism data. A pronounced change in the amount and incidence of astigmatism occurs between 1 year of age and later. Although we selected patients with an astigmatism ≥1·0 D at 1 year of age, there were a few cases with an astigmatism of 0·5 (Fig. 2). The reason was that we selected patients with an astigmatism ≥1·0 D in at least one eye and we used only the right eyes for the calculations. The selection criterion was in these cases fulfilled by the other eye. Between the first and second measurement the astigmatism vanished in one-sixth of the infants. At the age of 4 one-third of the patients had a purely spherical refraction. There was a general shift of the distribution towards lower astigmatic values through the test period, although there were some cases with high cylindrical refractive errors (≥2·5 D) both at the beginning and at the end of the test period.

The axis of the majority of the astigmatic infants (n=272) was plus cylinder axis 180±15°, and it remained unchanged during the follow-up period. At the age of 1 there were 18 cases with astigmatism axis in 90±15° and 10 cases with oblique axis. No eye showed a variation of the cylinder axis greater than 15° during the test period.

In 2% of the infants there was no change in either the amount of cylindrical refraction or in axis during the four years of examination.

The findings on the astigmatism of the 18 cases with axis in 90±15° are presented in Fig. 2B. The age induced changes in distribution of the astigmatism of this subgroup differ from the data presented in Fig. 2A. The changes in distribution are small and the changes of astigmatism with age are limited. The astigmatism of the cases with oblique axis showed a decrease with age in the majority of cases (Fig. 2C).

In order to evaluate the individual changes in astigmatism during the follow-up period we selected two subgroups for further analysis—one group of patients with an astigmatism ≥2·0 D at the initial test session (n=30), and another with patients with no

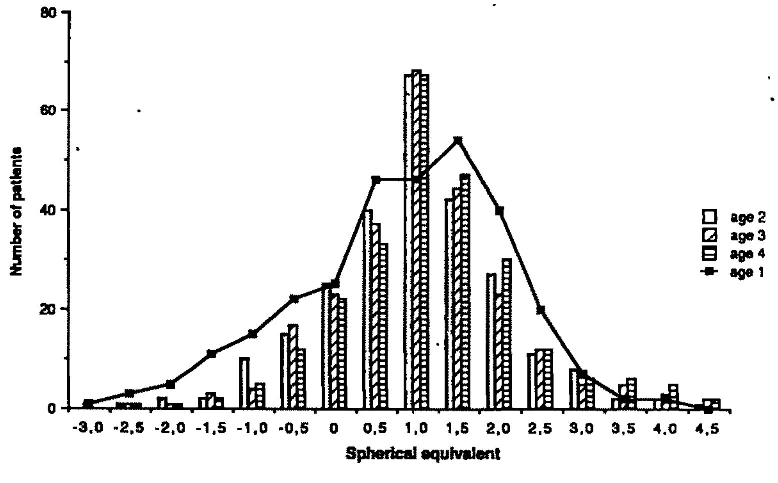

Fig. 1 *The distribution of the spherical equivalent at one-year intervals between 1 and 4 years of age.*

cylindrical errors at the last test session at 4 years (n=89). In general the infants with an initial astigmatism $\geqslant 2{\cdot}0$ D showed a decrease of their cylindrical refractive errors at 4 years of age (Fig. 3A). There were, however, some patients (nine out of 49) in this group who had an increasing astigmatism as they grew older. Among them were more infants with a plus cylinder axis of 90° than would be expected (n=5). Most of the cases in the latter group with no cylindrical error at 4 years had an initial astigmatism of 1·0 D, but there were cases with as much as 2·5 D at 1 year of age (Fig. 3B).

11% (n=33) of the astigmatic patients had an anisometropia of 1·0 D or more in either meridian at the age of 1 year. At the age of 4, 10% (n=30) had an anisometropia of 1·0 D or more. The majority of cases (n=19) with anisometropia at the age of 1 that showed no anisometropia at the age of 4 were replaced at the measurements at the age of 4 by 16 cases with no anisometropia at the age of 1 year. The anisometropic patients at both age 1 and 4 years were significantly more likely to have an astigmatism of 1·5 D or more, 80% ($p<0{\cdot}001$, t test) at the age of 1 and 84% ($p<0{\cdot}001$, t test) at the age of 4.

When we closely examined the 19 patients who had anisometropia at the age of 1 but not at the age of 4,

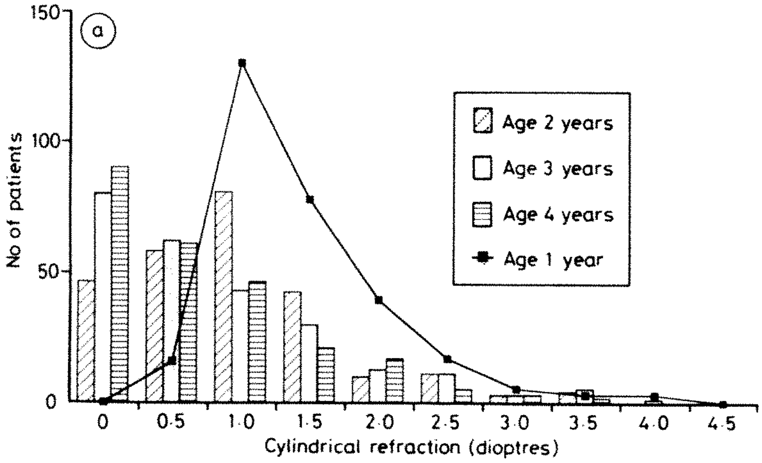

Fig. 2A

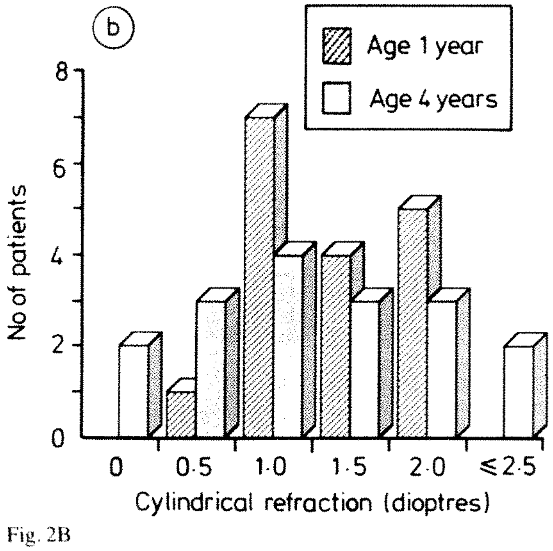

Fig. 2B

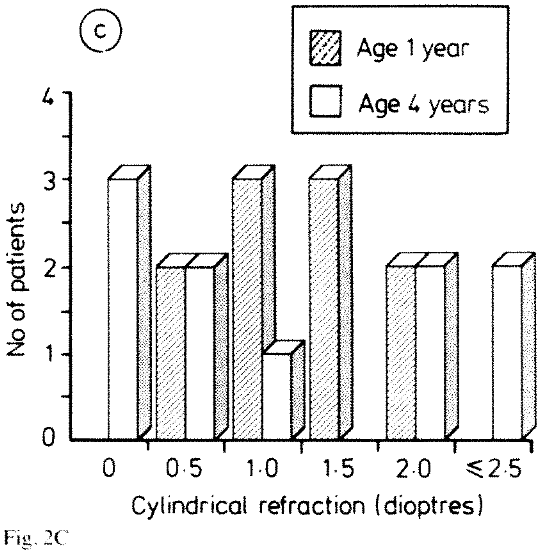

Fig. 2C

Fig. 2 A: *Distribution of the cylindrical refractive error at the four-yearly test sessions. In* B *and* C *the cylindrical refractive power at the age of 1 and 4 years for the patients with with-the-rule astigmatism* (B) *and oblique astigmatism* (C) *are presented.*

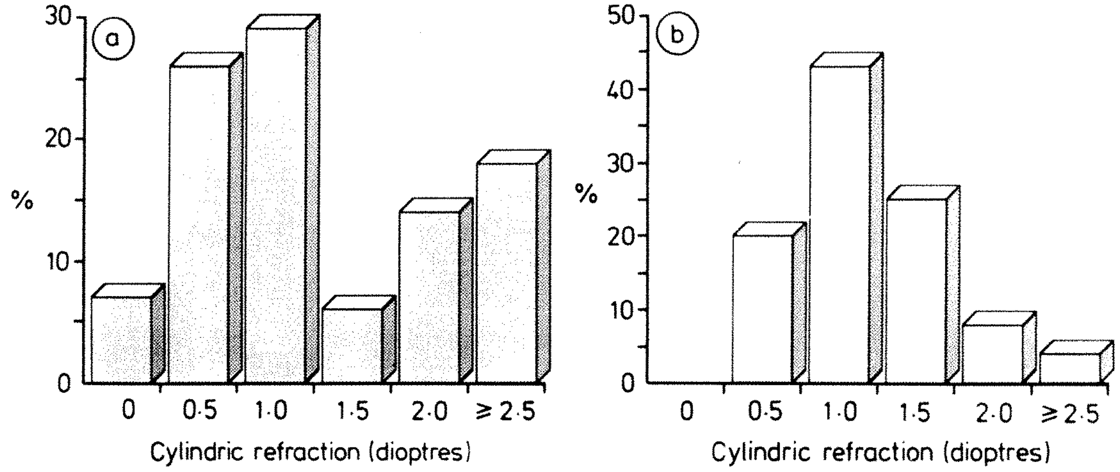

Fig. 3A

Fig. 3B

Fig. 3 A: *Distribution of the cylindrical refraction at the age of 4 years of all infants with a astigmatism ≥2·0 D at the age of 1 year.* B: *Distribution of the astigmatism at the initial measurement at 1 year of age of all children with disappearance of astigmatism at the age of 4 years.*

we found that there was an emmetropisation as well as a conversion of astigmatism to spherical refraction. The magnitude of these two processes is greatest in the most hyperopic eyes. In the 16 patients who had anisometropia that did not show up until the age of 4 there was emmetropisation but no conversion of astigmatism to spherical refraction. This group had, in general, a more hyperopic spherical equivalent refraction than the total sample.

Discussion

The present study provides longitudinal data on the change in cylindrical refractive power and axis of astigmatism during infancy and early childhood. Our data are in agreement with those of previous studies[3 7 10] in that the astigmatism decreases as the infant grows older. This change is especially notable in the amount and incidence of astigmatism between the first and second year of life.[7] During the same period the spread of the distribution of the spherical equivalent is markedly reduced. These results agree with Fabian's theory[11] of emmetropisation. It is notable that, although there is a continuous reduction of astigmatism throughout the test period, there are only small changes in the distribution of the spherical equivalent after the second year of life. The cylindrical refractive error must be converted into a spherical refractive error.

In infants the predominant form of astigmatism is plus cylinder axis of 180±15° as shown in this study for about 90% of the eyes, whereas after the age of 6 the predominant form is plus cylinder at 90±15°.[2] In our data no evidence for changes in axis with age was found, indicating that the axis remains constant. To our knowledge there is no longitudinal study which shows a change in axis with age, while there are cross-sectional data[2] demonstrating an increasing number of with-the-rule astigmatism (cylindrical axis of 90°) and a decreasing number of cases with against the rule astigmatism as the children grow older.

To explain this we need to study the selection criteria. In our longitudinal study infants who had astigmatism at the initial test session were followed up. In this group there is a decreasing incidence of astigmatism and no axis changes during the follow-up period. The probable conclusion from the results of our study is that the astigmatic cases with plus cylinder axis of 90° found at school age are probably children who acquire their astigmatism at the age of 3 or 4 or later. To examine this phenomenon more closely a longitudinal study must be performed with a large sample of children who are unselected with respect to their refractive status at the beginning of the study.

An important finding in both the group with with-the-rule astigmatism and the group with oblique astigmatism was that there are cases with an increasing astigmatism as well as an increasing spherical equivalent refraction with age. This phenomenon was not found in the group with against-the-rule astigmatism. This indicates that patients with with-the-rule and oblique astigmatism at the age of 1 year need a special follow-up.

In agreement with the data presented by Ingram and Barr[12] we found an association between anisometropia and astigmatism and that approximately 50% of the anisometropic cases are exchanged during follow-up. This relation was significant at both the age of 1 and 4 years. It is important to note that the subgroups with anisometropia in combination with astigmatism are unstable.

In summary, our study showed that dynamic changes occur in astigmatism and anisometropia during infancy. Although the majority of cases show a decrease in magnitude of astigmatism between 1 and 4 years, some children show an astigmatism that is stationary or even increasing.

The special subgroups of astigmatic eyes at risk of amblyopia or squint or both must be studied further, and the instability of astigmatism and anisometropia have to be taken into consideration before spectacles are prescribed for very young children.

This work was supported by Swedish Medical Research Council (grant 02226), the Samaritan Foundation, and the handlanden H. Svensson foundation.

References

1 Mohindra I, Held R, Gwiazda J, Brill S. Astigmatism in infants. *Science* 1978; **202:** 329–30.
2 Gwiazda J, Scheiman M, Mohindra I, Held R. Astigmatism in children: changes in axis and amount from birth to 6 years. *Invest Ophthalmol Vis Sci* 1984; **25:** 88–92.
3 Fulton AB, Dobson Y, Salem D, Mar C, Petersen RA, Hansen RM. Cycloplegic refraction in infants and young children. *Am J Ophthalmol* 1980; **90:** 239–47.
4 Howard HC. Infant eyes: optics and accommodation. *Curr Eye Res* 1982; **2:** 217–24.
5 Howland HC, Atkinson J, Bradick O, French J. Infant astigmatism measured by photorefraction. *Science* 1978; **202:** 331–2.
6 Hirsch MJ. Changes in astigmatism during the first eight years of school: an interim report from the Ojuai longitudinal study. *Am J Optom* 1963; **40:** 127–32.
7 Atkinson J, Bradick O, French J. Infant astigmatism: its disappearance with age. *Vision Res* 1980; **40:** 891–3.
8 Mohindra I, Held R. Refraction in humans from birth to 5 years. *Doc Ophthalmol Proc Ser* 1981; **28:** 19–27.
9 Lindner G. *Die Bestimmungen des Astigmatismus durch die Schatteprobe mit Zylindergläsern*. Berlin: Karger, 1927.
10 Dobson V, Fulton AB, Sebris SL. Cycloplegic refraction of infants and young children: the axis of astigmatism. *Invest Ophthalmol Vis Sci* 1984; **25:** 83–7.
11 Fabian G. Ophthalmological serial examination of 1200 children in the second year of life. *Acta Ophthalmol (Kbh)* 1966; **49:** 473–9.
12 Ingram RM, Barr A. Changes in refraction between the ages of 1 and 3½ years. *Br J Ophthalmol* 1979; **63:** 339–42.

Accepted for publication 4 December 1986.

British Journal of Ophthalmology, 1988, **72**, 150–154

Drug delivery through soft contact lenses

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SUMMARY Clinical studies were conducted on 466 patients waiting for senile cataract surgery and receiving chloromycetin, gentamicin, or carbenicillin subconjunctivally and through New Sauflon 70 and New Sauflon 85 lenses. The aqueous drug levels were biologically estimated at various time intervals. Soft contact lenses provided significantly higher drug penetration than subconjunctival therapy. Both modes of treatment provided therapeutically effective levels against most of the common ocular pathogens for varying intervals of 2 to 12 hours.

Soft contact lenses were initially used for drug delivery by Sedlavek in Czechoslovakia in 1965,[1] and since then many workers have advocated their use with various drugs. The hydrogel lenses, by virtue of their high water content and large intermolecular pore size, absorb water soluble drugs with some correlation with molecular weight, releasing them initially in a high pulse and then gradually, thereby complying with first order kinetics. However, the first order kinetics can be advantageously turned into practically zero order kinetics where sustained high concentration of the drug is obtained by superinstillation of drops at two- to four-hour intervals or reapplication of a soaked lens, depending on the need and severity of the condition.[2]

Anterior segment inflammations, whether infective or allergic, and angle closure glaucoma are a few of the important clinical conditions requiring a high intraocular concentration of drugs. The drugs which can be conveniently delivered are the water soluble antibiotics, steroids (betamethasone, dexamethasone, and prednisolone), pilocarpine, atropine, and homatropine.

The author has conducted various sets of clinical studies with the following aims: (1) to estimate and compare the penetration of various antibiotics into the aqueous after subconjunctival injection and soft contact lens delivery in relation to dosage and time; (2) to compare the drug penetration with hydrogel lenses of different water content.

Material and methods

The studies were conducted on 466 patients awaiting surgery for senile cataract. Eyes suffering from any kind of disease were not included in this study. The time of cataract incision was so planned as to provide a predetermined dose-to-sample time interval.

In the subconjunctival group of cases the specified dose of antibiotic dissolved in 0·5 ml of distilled water was injected subconjunctivally, and the cases were divided into various subgroups depending on the dose-to-sample interval which varied over ¼, ½, 1, 2, 4, 8, and 12 hours.

In the other group of cases soft contact lenses were used to deliver the drugs. The lenses employed were of two different water contents, namely, New Sauflon 70 and New Sauflon 85 (supplied by CLM, London). These lenses were afocal, of uniform thickness (0·2 mm), and of uniform diameter (14·0 mm); they had varying base curves of 8·0 to 9·0 mm. Each lens was soaked for half an hour in freshly prepared 0·5 ml solution containing the specified dose of antibiotic. Thereafter the lens was taken out, placed on a sterile filter paper for 5 seconds, applied to the anaesthetised cornea for half an hour, and then removed. Aqueous samples were collected at the time of operation and at various time intervals, namely, ¼, ½, 1, 2, 4, and 6 hours in different groups of patients.

Subconjunctival group (224 eyes). Drug doses and number of eyes studied: (*a*) chloromycetin sodium succinate 50 mg (65 eyes); (*b*) carbenicillin 50 mg (69 eyes); (*c*) gentamicin sulphate 20 mg (90 eyes).

Soft contact lenses group (242 eyes). Drug doses and number of eyes studied: (1) New Sauflon 70 lenses—(*a*) chloromycetin sodium succinate 50 mg (55 eyes), (*b*) carbenicillin 50 mg (35 eyes); (2) New Sauflon 85 lenses—(*a*) carbenicillin 50 mg (42 eyes), (*b*) gentamicin sulphate 20 mg (60 eyes), (*c*) chloromycetin sodium succinate 50 mg (50 eyes).

After aspiration of aqueous samples, the bio-

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Table 1 *Mean aqueous concentration of various antibiotics at various time intervals after subconjunctival injections and the use of soft lenses (Sauflon 70 and 85) in 466 eyes*

Time interval in hours after removal of lens and after subconjunctival injection	*Antibiotic penetration (μg/ml with SD)*							
	Chloromycetin 50 mg			*Carbenicillin 50 mg*			*Gentamicin 20 mg*	
	Subconj. inj.	*Sauflon 70*	*Sauflon 85*	*Subconj. inj.*	*Sauflon 70*	*Sauflon 85*	*Subconj. inj.*	*Sauflon 85*
¼	4·35 ±2·21	11·25±1·13	24·14±2·24	38·8± 6·69	81·9±17·92	148·60±26·64	3·53±1·78	10·79±0·601
½	13·275±4·93	19·35±4·13	29·75±0·74	80·5±10.90	70·1±21·13	136·40±12·62	5·14±2·10	35·25±6·750
1	16·24 ±1·92	13·20±2·57	22·10±3·70	69.5± 7·36	31·3± 6·25	64·20±14·37	14·62±1·92	21·38±2·242
2	12·275±1·90	9·75±2·32	6·75±1·88	32·0± 6·99	6·8± 1·89	28·0 ± 9·41	12·42±2·84	12·50±2·953
4	10·215±1·05	Nil	4·66±1·29	12·9± 4·10	Nil	Nil	10·21±4·68	6·13±0·840
6	ND	—	Nil	ND	—	—	ND	1·75±1·00
8	4·325±0·68	—	—	Nil	—	—	8·10±3·12	ND
12	Nil	—	—	Nil	—	—	6·64±1·28	—
18	—	—	—	—	—	—	Nil	—
24	—	—	—	—	—	—	Nil	—
No. of eyes	65	55	50	69	35	42	90	60

ND=Not done.

estimation was done by a modified disc diffusion method using *Bacillus subtilis* NCIM 2062 as the assay organism.

Results

Table 1 shows the mean values of antibiotics with standard deviation in the aqueous at various time intervals after subconjunctival injection and the use of Sauflon 70 and Sauflon 85 lenses (466 eyes).

It is notable that, after subconjunctival injections, the antibiotics penetrated within 15 minutes, attained their maximum concentration within 30 to 60 minutes, and thereafter declined, but maintained quite a high concentration up to four hours. They were not traceable in samples collected at 8 to 18 hours. It is also evident from Table 1 that soft contact lenses provided very high penetration into the aqueous within 15 minutes; the drugs attained their peak level within 30 minutes and thereafter rapidly fell. Within four to six hours the samples were almost free of antibiotics.

Figs. 1, 2, and 3 show comparative concentrations of different antibiotics when given subconjunctivally and through soft contact lenses. It is notable that with soft contact lenses the peak concentration of antibiotics in aqueous occurred quickly, but it showed a rapid decline as compared with the subconjunctival group. Sauflon 85 provided almost double the drug penetration in the first three samples collected up to one hour as compared with Sauflon 70. After one hour the deline in the Sauflon 85 group was too rapid, and there was hardly any difference in the duration of penetration in soft lenses of different water content.

Discussion

Because of tear flow, topically instilled drugs have a limited life span in the conjunctival sac, and only a fraction of their mass penetrates the eyeball across the epithelial barrier of the cornea. The resistance of corneal epithelium to ions is about 2000 times that of the total stroma. The relative thickness of epithelium, stroma, and endothelium is 0·1:10:0·01, and the relative resistance to diffusion of electrolytes by these structures is 2000:1·0:10·0. This results in drug penetration in many cases in quantities which is below the optimum required for treatment.[3,4] Drug penetration may be marginally improved by retention of the instilled drug for slightly longer in the conjunctival sac, by frequent instillation, by increasing the viscosity of the drug with methylcellulose or polyvinyl alcohol as a vehicle, by using the drug in ointment or suspension form, or by making the drug more alkaline.[5]

However, much better penetration can be achieved by prolonging the contact time of the drug in the eye. Hydrophilic contact lenses as an adjuvant to drug delivery have given results.[6-9] Drugs penetrate hydrophilic contact lenses at a rate which depends on the pore size between the cross linkages of the three-dimensional lattice structure of the lens, on the concentration of the drug in the solution, and on the molecular size of the drug.[10] Waltman and Kaufman[11] used fluorescein as a model drug with bionite (Griffin) and Soflens (Bausch and Lomb) lenses in rabbit eyes and observed that the amount of drug taken up by a lens varied with the material of the lens, primarily depending on its water content.

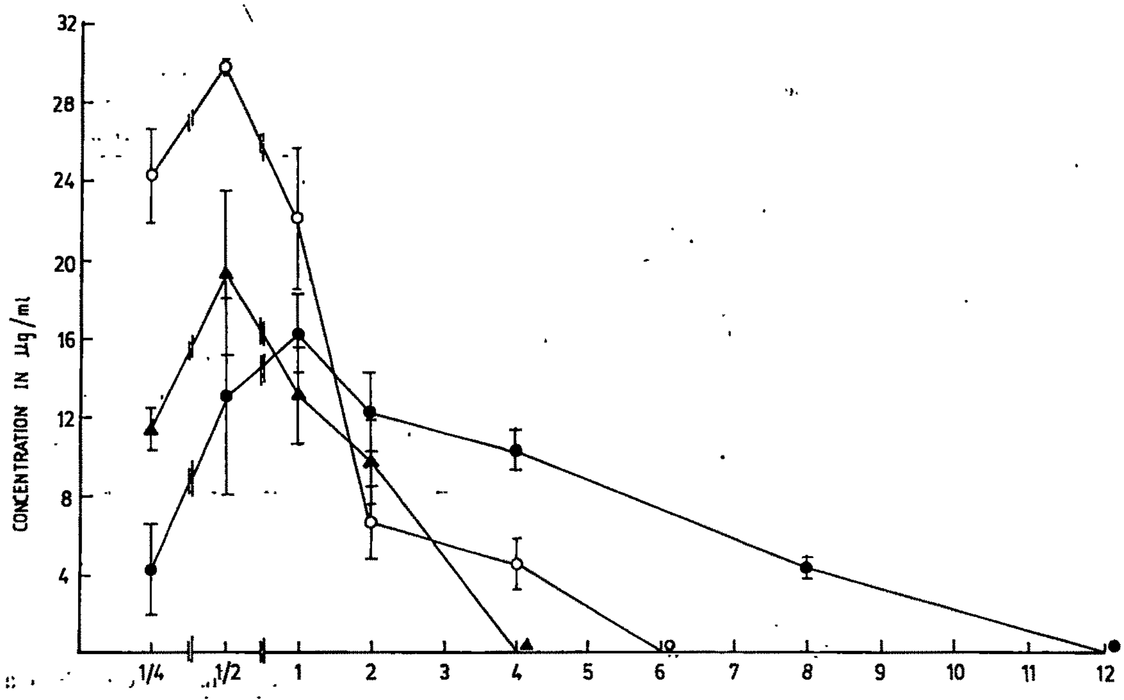


Fig. 1 *Comparative levels of chloramphenicol in 170 eyes.* ●*=Subconjunctival injection.* ▲*=Sauflon 70.* ○*=Sauflon 85.*

Most of the studies of soaking time have been confined to pilocarpine solution only. Podos *et al.*[12] observed that with a 0·5% solution of pilocarpine the drug uptake appears to increase with the time of immersion, approaching a maximum after soaking the lens for 30 to 60 minutes. Preliminary biochemical studies conducted by Hillman[10] showed that approximately 24 hours' soaking is necessary to saturate a Sauflon lens, which then holds 400 to 500 µg of pilocarpine.

The release rate of pilocarpine from the soft lens in vivo and in vitro has an approximate half life of 30 minutes, and almost all the pilocarpine is leached out after four hours of lens wear.[10] In contrast to a 2-minute soak advocated by Podos *et al.*[12] a 30-minute soak was used in the present study, because Hillman[10]

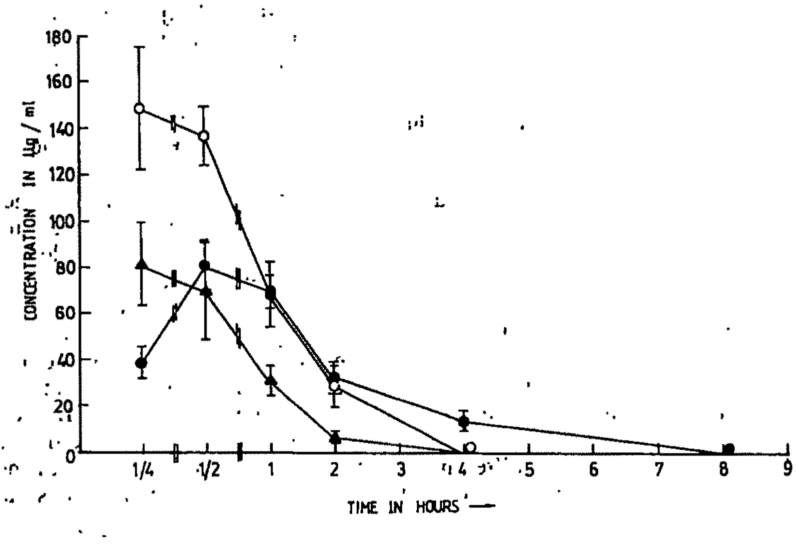


Fig. 2 *Comparative levels of carbenicillin in 146 eyes. Symbols as in Fig. 1.*

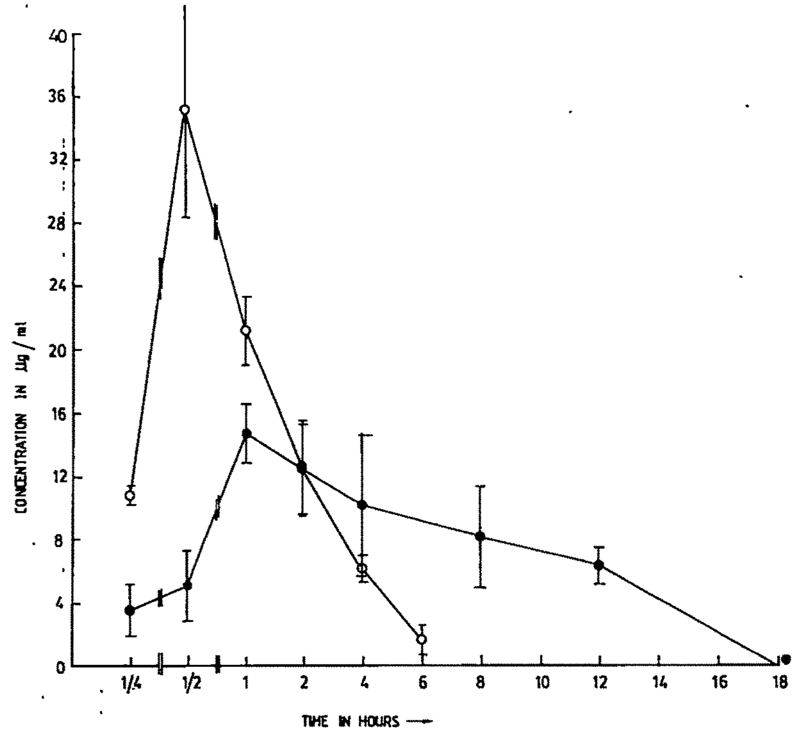


Fig. 3 *Comparative levels of gentamicin in 150 eyes. Symbols as in Fig. 1.*

observed that a 30-minute soak allows equilibration throughout the lens, so that when the drug diffuses out from the surface layers it is replenished from the deep part of the lens, which acts as a reservoir producing a more sustained high yield. Hillman[10] further observed that a prolonged soak to a state of equilibrium produced a more standardised form of presoaked lens. Half an hour's wear was practised in the present study, since Podos *et al.*[12] concluded that this period is the shortest that will provide maximum concentration of the drug to ocular tissues.

Subconjunctival therapy is the most widely practised, for it provides quick and prolonged penetration of water soluble drugs into the aqueous. The advantage of subconjunctival injection is that it short-circuits the essential barrier set up by the epithelium of the cornea and conjunctiva to the entrance of substances into the eye. The permeability of the sclera corresponds to and is even greater than that of the corneal stroma.[13-15] The corneal stroma allows diffusion of most solutes under a certain molecular weight with a cut-off point of 50 000.[4]

Absorption into the interior of the eye is essentially a process of diffusion through the tissues, not, as is sometimes said, through the circulation. This fact has been proved by an observation where better intraocular concentration was noted in a freshly killed animal than in a living animal and by the fact that the addition of a vasoconstrictor drug increases the penetration.[13] Corneal stroma also permits easy diffusion of subconjunctivally injected fluid, as it bypasses the barrier of corneal epithelium.[16] The observed aqueous humour concentration of the subconjunctivally injected drugs (Table 1) is almost double the reported minimum inhibitory concentration (Table 2)[17] against most of the common ocular pathogens. In such concentrations some antibiotics

Table 2 *Minimum inhibitory concentration of gentamicin, carbenicillin, and chloramphenicol required for common ocular pathogens*[17]

Organisms	*Gentamicin in µg/ml*	*Carbenicillin in µg/ml*	*Chloramphenicol in µg/ml*
Staph. aureus	0·12–4·0	0·5 (for non-penicillinase producing) 50·0 (for penicillinase producing)	4·0
Klebsiella spp.	1·0–2·0	200·00	1·0
Proteus spp.	2·0	2·0–5·0	6·0–12·0
Escherichia coli	2·0	5·0	2·0
Pseudomonas aeruginosa	1·0–8·0	50–125	Mainly resistant

such as chloramphenicol, which is essentially bacteriostatic, may act as a bactericidal drug for varying intervals of time.[18] However, the therapeutic level lasts for only six to eight hours, and hence in severe infections the subconjunctival therapy may have to be repeated twice or thrice to provide consistently high drug concentrations.

MERITS OF SOFT LENS DELIVERY SYSTEM

A distinct merit of the soft lens delivery system is the higher drug penetration than by subconjunctival therapy. In agreement with Waltmann and Kaufman[11] we noted that the drug penetration was significantly greater when lenses of higher water content were used. These observations may favour the use of this mode of treatment when high intraocular penetration of drug is needed. Another notable merit of the hydrogel delivery system may be the need for much smaller amounts of drugs to produce the desired therapeutic levels.[9,19] Since less drug is delivered to the eye per unit of time, fewer side effects may be expected. Thus drugs that previously could not be used because of adverse side effects or excessive toxicity might be considered for therapeutic use at lower concentration.[19] A more obvious advantage is to those patients who are apprehensive about a prick in the eye, which can cause some ocular discomfort or pain or chemosis or even subconjunctival haemorrhage, especially when repeated injections are needed.

DISADVANTAGES OF SOFT LENS DELIVERY SYSTEM

Drug release from a hydrogel contact lens is pulse-like, with an initial peak followed by a gradual decline (first order kinetics). This may necessitate repeated application of drug soaked lenses in cases which require consistently high drug penetration. In addition a proper fitting of a hydrogel contact lens is in itself a procedure not entirely devoid of complications and added expense. Moreover, prolonged wear of a contact lens may lead to intolerance, corneal vascularisation, lens deposits and spoilage, giant papillary conjunctivitis, lens loss, and corneal ulceration.

To conclude, it may be stated that the hydrogel contact lens delivery system may be an effective method of treating some of the infective conditions of anterior segments of the eye in patients who are not suitable for subconjunctival therapy or in whom there is a reason to use a minimum quantity of drug.

References

1 Sedlavck J. Possibilities of application of ophthalmic drugs with the aid of gel contact lens. *Cesk Oftalmol* 1965; **21:** 509–14.

2 Jain MR, Batra V. Steroid penetration in human aqueous with Sauflon 70 lenses. *Indian J Ophthalmol* 1970; **11:** 26–31.

3 Maurice DM. The permeability to sodium ions of the living rabbit cornea. *J Physiol (Lond)* 1951; **112:** 367–71.

4 Maurice DM. Structures and fluids involved in the penetration of topically applied drugs. *International ophthalmic clinics.* Boston: Little, Brown, 1960: **20:** 7–20.

5 Maurice DM. Factors influencing the penetration of topically applied drugs. *International ophthalmic clinics*. Boston: Little, Brown, 1980: **20:** 21–32.

6 Asseff CF, Weisman RL, Podos SM, Becker B. Ocular penetration of pilocarpine in primates. *Am J Ophthalmol* 1973; **75:** 212–5.

7 Hull DS, Edelhauser HF, Hyndiuk RA. Ocular penetration of prednisolone and hydrophilic contact lens. *Arch Ophthalmol* 1974; **92:** 413–6.

8 Kaufman HE, Uotila MH, Gasset AR, *et al.* The medical uses of soft contact lenses. *Ophthalmology* 1971; **75:** 361–73.

9 Marmion VJ, Jain MR. Role of soft contact lenses and delivery of drugs. *Trans Ophthalmol Soc UK* 1976; **96:** 319–21.

10 Hillman JS. Management of acute glaucoma with pilocarpine soaked hydrophilic lens. *Br J Ophthalmol* 1974; **58:** 674–9.

11 Waltman SR, Kaufman HE. Use of hydrophilic contact lenses to increase ocular penetration of topical drugs. *Invest Ophthalmol Vis Sci* 1970; **9:** 250–5.

12 Podos SM, Becker B, Asseff CF, Harstein J. Pilocarpine therapy with soft contact lenses. *Am J Ophthalmol* 1972; **73:** 336–41.

13 Duke-Elder S. *System of ophthalmology.* London: Kimpton, 1962: **8:** 514–6.

14 Jain MR, Srivastava S. Ocular penetration of hydrocortisone and dexamethasone into the aqueous humour after subconjunctival injection. *Trans Ophthalmol Soc UK* 1978; **98:** 63–5.

15 Wine NA, Gornall AC, Basu PK. Ocular uptake of subconjunctivally injected C-14 hydrocortisone. *Am J Ophthalmol* 1964; **58:** 362–5.

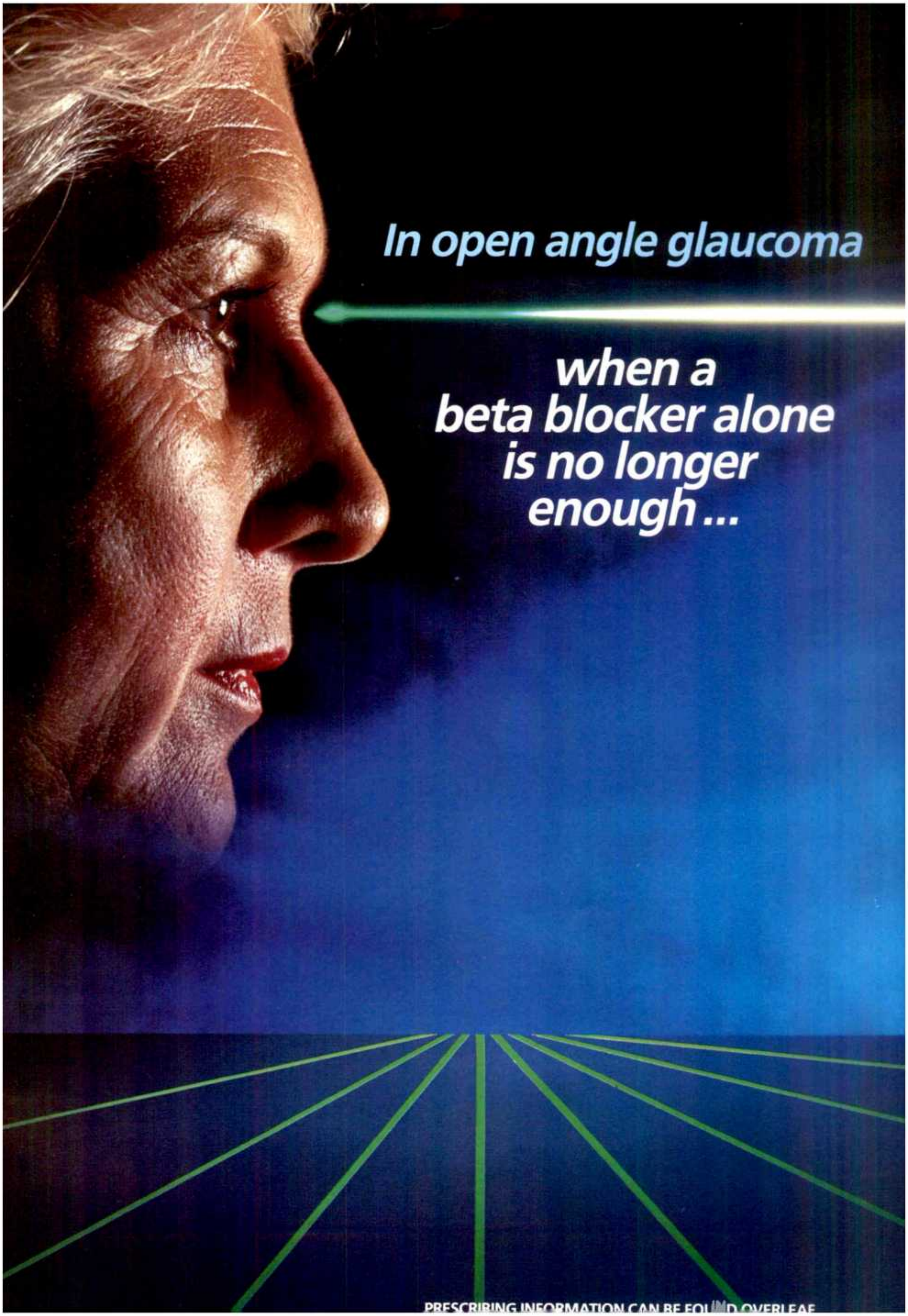
16 Friend J. Biochemistry of ocular surface epithelium. *International ophthalmology clinics*. Boston: Little, Brown, 1979: **19:** 73–91.

17 Briant MC. *Antibiotics and their laboratory control*. London: Butterworths, 1972: 10–14.

18 Smolin G, Thoft RA. *The cornea: antibiotic mechanisms.* Boston: Little, Brown, 1983: 134–43.

19 Lerman S, Reininger B. Simulated sustained release pilocarpine therapy and aqeous humour dynamics. *Can J Ophthalmol* 1971: **6:** 14–23.

Accepted for publication 15 December 1986.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Chronic alcoholism and microbial keratitis*

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SUMMARY In a series of 227 consecutive, non-referred patients with microbial keratitis an analysis of the accumulated hospital records showed that one-third were associated with chronic alcoholism. The diagnosis of alcoholism was usually unsuspected on admission to hospital. The microbial pathogenesis in these patients was distinctive; coagulase-negative staphylococci, α- and β-streptococci, moraxellae, enteric Gram-negative bacilli, and polymicrobial infections were unusually prominent. *Pseudomonas aeruginosa* was uncommon. Trauma, exposure, bullous keratopathy, other external ocular diseases, and self-neglect were the major recognised predisposing causes. The nutritional, toxic, and immunological sequelae of alcoholism may also have been contributory. Ophthalmologists should be alert to the diagnosis of chronic alcoholism in their patients. Chronic alcoholism may be an important and underrated risk factor for microbial keratitis.

It has been suspected that the pathogenesis and pattern of microbial keratitis in the chronic alcoholic may differ from that usually described and defined principally by an uncommonly high prevalence of moraxella infection.[1-4] However, no formal study has been undertaken. In one hospital based series of patients with a high rate of chronic alcoholism 45% of cases of microbial keratitis from 1965 to 1970 were caused by moraxellae.[3] Improvements in nutrition and sanitation were cited as possible explanations for the subsequent decline in moraxella prevalence at the same institution to 5% over the period 1971–4.[3] There may also have been important demographic factors, including alterations in the catchment area of the hospital,[1] to explain this change.

An accepted definition of chronic alcoholism is excessive, persistent drinking that interferes with the person's health, interpersonal relationships, legal position, or means of livelihood.[5] The diagnosis is often overlooked by health care professionals and should be specifically sought, particularly in high-risk groups.[6] In hospital based populations chronic alcoholism has been reported in 8 to 18% of US private hospital patients,[7,8] with even higher levels in metropolitan public hospitals in the USA and UK.[9-12] The rates in female inpatients have been reported to be one-third to two-thirds those of men.[8,9,11] An estimated 10% of the United States adult population is believed to have a drinking problem.[13-14]

Published series of patients with microbial keratitis have not recorded many alcoholics.[1-3] As Los Angeles County has one of the higher rates of alcoholism in the United States[15,16] we carefully studied the prevalence of chronic alcoholism in our retrospective cases of microbial keratitis so as to evaluate the pattern of ocular disease and gauge the particular problems of management.

Subjects and methods

A total of 227 consecutive patients with microbial keratitis were admitted to the Los Angeles County-University of Southern California Medical Centre (LAC-USC) over the 11-year period, 1 July, 1972 to 30 June, 1983. LAC/USC is a non-referral, primary care facility. The microbial aetiology of the corneal infections was investigated by standard techniques.[17-19] Bacterial keratitis was defined as an inflammatory infiltrate and ulceration of the corneal stroma, associated with an epithelial defect, from which one or more microbial species were cultured;

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*Presented in part at the Annual Spring Meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, 6–10 May, 1985.

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all but trace isolates were reported as positive. Ophthalmological, microbiological, and medical data were recorded, according to a detailed protocol, by reviewing the accumulated, hospital inpatient and outpatient charts from all specialities. As LAC-USC is the main primary-care institution for Los Angeles County, lifetime medical histories were frequently available.

Seventy-two individuals (32%) were diagnosed as chronic alcoholics, though the diagnosis was usually unsuspected during the ophthalmic admission. Admissions to the inpatient detoxification service were recorded in many patients' charts. In other instances the diagnosis had been based on a combination of the social and behavioural history, clinical signs, and biochemical findings, or the finding of major medical complications of chronic alcoholism.

Results

The racial distribution of the alcoholic group (72 patients) was: 54% white; 28% black; 12% hispanic. It contrasts with that of the non-alcoholic patients (155 patients): 27% white; 22% black; 40% hispanic. Sixty-six patients were male and there were six females. Forty-four left eyes and 28 right eyes were involved. Ulcers were small (<2 mm) in five cases, moderate (2–6 mm) in 50, and large (>6 mm), in 17 cases. There was more than a six-fold difference in prevalence between the months of highest (January) and lowest (February and August) incidence.

To investigate the nature of the alcoholic group we investigated the lifetime incidence of several major medical complications of chronic alcoholism; the results are shown in Table 1. Two patients also had a history of narcotic drug abuse, four patients suffered from a severe psychotic or major affective disorder, and four patients were diabetic. Trauma was implicated as a factor in 23 patients (32%) and local ocular disease in 33 (46%). One-fifth had either bullous keratopathy or ocular exposure. It is noteworthy that no predisposing factors were recorded in 25 patients (35%).

Table 1 *Recorded lifetime incidence of major medical complications of chronic alcoholism*

	Percentage	*Number*
Itinerancy	19	14
Delirium tremens	22	16
Seizure disorders	18	13
Acute and chronic brain syndromes*	15	11
Hepatic cirrhosis (biopsy-proved)	15	11
Known death from hepatic complications	10	7
Chronic pancreatitis	4	3

*Includes Wernicke's encephalopathy, alcoholic dementia, cerebellar degeneration, and Korsakoff's psychosis.

Fifty-nine (82%) of the 72 alcoholic patients were culture-positive, and 32% of these cultures showed polymicrobial infection. The remarkable features of the microbiological spectrum (Table 2) were the higher than normal prevalences of coagulase-negative staphyloccoci,[126] α- and β-haemolytic streptococci, *Moraxella* spp., and enteric Gram-negative bacilli. *Pseudomonas aeruginosa* was surprisingly uncommon and found in only four patients (6%). Fungi were also uncommon.

Table 3 compares the rates of complications and operations between the alcoholic and non-alcoholic patients. There was a tendency for more severe disease in chronic alcoholics. Self-neglect was probably an important factor. Whereas 52% of the non-alcoholic group presented to an ophthalmologist within 72 hours of developing symptoms, only 21% of the chronic alcoholics had reported by this time. In fact 42% of the alcoholics did not seek medical attention for at least one week. It was notable that a significant minority complained of little or no pain.

Table 2 *Microbial causation of corneal ulcers in a population of chronic alcoholics*

	*Percentage of Patients**	*Numbers*†*
Gram-positive cocci		
Coagulase-negative staphylococci	28	20 (4)
Staphylococcus aureus	15	11 (7)
Streptococcus pneumoniae	13	9 (4)
β-haemolytic streptococci	11	8 (3)
α-haemolytic streptococci	7	5 (5)
γ-haemolytic streptococci	1	1 (1)
Microaerophilic streptococcus	1	1 (0)
Gram-positive bacilli		
Bacillus subtilis	1	1 (0)
Clostridium spp.	1	1 (0)
Gram-negative cocci/coccobacilli		
Moraxella spp.	13	9 (5)
Branhamella catarrhalis	1	1 (0)
Gram-negative bacilli		
Proteus spp.	7	5 (2)
Pseudomonas aeruginosa	6	4 (1)
Enterobacter spp.	4	3 (3)
Citrobacter spp.	3	2 (0)
Klebsiella spp.	1	1 (1)
Other *Pseudomonas* spp.	1	1 (0)
Aeromonas spp.	1	1 (1)
Haemophilus influenzae	1	1 (1)
Fungi		
Candida albicans	1	1 (1)
Penicillium spp.	1	1 (1)
Cladosporium spp.	1	1 (1)
Negative cultures	18	
Polymicrobial cultures	32	

*n=72. †Figures in parentheses indicate the number of polymicrobial infections.

Table 3 *Comparisons of rates of complications and operations in microbial keratitis in chronic alcoholic and non-alcoholic patients*

	Chronic alcoholic group (72)	*Non-alcoholic group (154)*
Hypopyon	33%	33%
Descemetocoele/perforation	22%	15%
Perforation occurring >3 days after admission	8%	4%
Penetrating/lamellar keratoplasty	18%	12%
Glue/soft contact lens	11%	5%
Enucleation/evisceration	6%	6%
Soft contact lens/epithelial failure	4%	4%
Mean admission time in days (±SD)	17·6 (±12·7)	14·4 (±10·9)

Discussion

Chronic alcoholism was the most prevalent association identified in 227 consecutive patients admitted to LAC-USC with microbial keratitis. As these chronic alcoholics were admitted for ophthalmological treatment and not for alcoholism, it is remarkable that the available lifetime incidence figures of alcohol-related physical diseases were closely comparable to data from metropolitan alcoholic units.[20-24] This lends support to the methodology but, more importantly, suggests that chronic alcoholism may be a major unsuspected risk factor for microbial keratitis. The alcoholism had usually been overlooked during the ophthalmic admission, as it may have been in other series of microbial keratitis patients.

The pathogenesis of microbial keratitis in chronic alcoholics is undoubtedly multifactorial (Table 4). A history of trauma was obtained in one-third of the cases. That trauma played a significant part in this study was also suggested by the predominance of keratitis in left eyes (interpersonal trauma is more usually inflicted with the right hand) and perhaps by the high prevalence of keratitis in the post-Christmas period. Amnesia, mental illness, and deliberate evasion may contribute to an underassessment of the role of trauma in chronic alcoholics, and may account for many of the patients in whom no predisposing factor was recorded (35%). A primary predisposition for chronic alcoholism per se cannot be excluded.

Self-neglect is emphasised by the duration of symptoms at presentation. Coexisting external ocular disease was important, and bullous keratopathy or ocular exposure were particularly common. The relative contribution of poor hygiene was impossible to quantify. An altered ocular microbial flora has also been reported to occur in alcoholics,[3] though we have no contributory data.

Table 4 *Aetiology of microbial keratitis in chronic alcoholics*

1. Trauma
2. Exposure during inebriation
3. External ocular disease
4. Poor hygiene
5. Altered conjunctival flora
6. Neglect
7. Malnutrition
8. Immunosuppression

There is a well documented increase in several kinds of systemic infectious diseases in chronic alcoholics, an associated increase in duration and severity of infection, and an increased mortality.[25] The causation is complex. Acute, reversible alcohol-induced lymphoid toxicity interrelates with protein-calorie, vitamin, and mineral malnutrition, as well as the chronic immunosuppressive effects of both chronic liver disease and chronic alcoholism per se.[23 25] The immunological deficits that may sometimes be important contributors to this increased risk of infection have recently been reviewed by Adams and Jordan.[25]

Such factors presumably had some role in the distinctive spectrum of microbial keratitis seen in our alcoholic patients, compared with those in the non-alcoholic group (unpublished data) and in other series.[1 17 26 27] Infections involving the usual causative organisms (*Staph. aureus*, *Str. pneumoniae*, and *Pseudomonas aeruginosa*) accounted for only 30% of the total. There was an increased prevalence of infections caused by such relatively uncommon corneal pathogens as *Moraxella*, α- and β-streptococci, and the enteric Gram-negative bacilli. This pattern of infection by organisms with usually low virulence for the cornea was not found in our non-alcoholic patients. It provides indirect evidence to support a significant pathogenetic role for the coagulase-negative staphylococci,[28 29] which were the most commonly isolated organisms. The pneumococcus was also more prevalent than in recent series.[1 17 26 27]

It was not possible to reanalyse the microbiological data by the more stringent criteria that have been recently suggested to increase the discrimination from tear film contamination.[30] However, even if the usual conjunctival commensal organisms were to be disregarded (coagulase-negative staphylococci, *Bacillus* and *Branhamella* spp.), we believe unjustifiably, 18% of the cases must still be considered polymicrobial, a genuinely high prevalence.[30]

The management of microbial keratitis associated with chronic alcoholism presents a formidable challenge, particularly in the decompensated alcoholic. The alcohol withdrawal syndromes, nutritional deficiencies, and medical complications must be treated urgently and expectantly.[3 21 23] The alcoholic patient's co-operation is often difficult to achieve. A sympathetic understanding of the psychopathology of chronic alcoholism, prodigious patience, and abundant time is necessary to gain the co-operation of many patients before optimal antibiotic therapy[17] can be carried out. If frequent high-dose, topical antibiotic therapy is not psychologically tolerated, we recommend that therapy be centred on regular subconjunctival antibiotic injections, performed through a 0·25 ml subconjunctival bleb of 2% lignocaine, after prior anaesthesia of the conjunctiva with topical 4% cocaine. This is supplemented with as much topical treatment as can be given.

There were increased rates of complications and operations among the chronic alcoholics. The use of isobutyl cyanoacrylate tissue glue for established or incipient corneal perforation is particularly valuable in this situation. As follow-up in decompensated alcoholics is frequently non-existent, we suggest that keratoplasty should generally be performed as a last resort and principally for tectonic reasons, unless there are favourable psychosocial factors or the patient is uniocular.

A diagnosis of chronic alcoholism may be easily overlooked.[5 9–12 21] Alcoholics who request treatment at general hospitals are prone to minimise their reports of alcohol consumption and deny their alcohol dependence. A recent study at a large medical centre showed that most of the physicians and nurses gave only cursory attention to patients' alcohol histories.[31] When alcoholism was perceived, physicians frequently still neglected their patients' alcohol dependency.[31] There is recent evidence from a study in Edinburgh that even a single session of counselling about alcohol abuse (during a medical admission) can significantly improve the alcoholic outcome at one year.[32] It should be the goal of all physicians actively to solicit their chronic alcoholic patients to take appropriate treatment before irreversible physical or psychological problems develop.

An alcohol history should be taken from every patient with microbial keratitis. A good indication can be gained by asking what the patient has drunk in the previous week. If the answer is nothing, the patient is unlikely to be an active alcoholic. Several brief alcoholism screening questionnaires have been devised.[33] Alternatively, discriminant questions can be asked independently concerning the quantity and frequency of drinking,[12] domestic arguments over drinking, possible fights while drinking, feelings about excessive drinking, morning drinking, and binges, and whether there have been work difficulties, loss of friends, arrests, or financial difficulties resulting from alcohol abuse.[21 31] An interview with a spouse or close contact can also be revealing.

It is important for ophthalmologists to address the problem of chronic alcoholism in their patients and assume responsibility for its identification. Our data suggest that microbial keratitis patients are a high-risk group for chronic alcoholism. Alcoholic screening can be easily incorporated into ophthalmic history taking, particularly in cases of microbial keratitis, ocular trauma, and optic neuropathy. Preventive care of the external eye would also probably reduce the toll of microbial keratitis in the chronic alcoholic.

This work was supported in part by a grant from Research for the Prevention of Blindness (Dr Smith).

References

1 Asbell P, Stenson R. Ulcerative keratitis. Survey of 30 years laboratory experience. *Arch Ophthalmol* 1982; **100:** 77–80.
2 Fedukowicz H, Horwich H. The Gram-negative diplobacillus in hypopyon keratitis. *Arch Ophthalmol* 1953; **49:** 202–11.
3 Baum J, Fedukowicz HB, Jordan A. A survey of moraxella corneal ulcers in a derelict population. *Am J Ophthalmol* 1980; **90:** 476–80.
4 Stern GA. Moraxella corneal ulcers: poor response to medical treatment. *Ann Ophthalmol* 1982; **14:** 295–8.
5 West LJ, Maxwell DS, Noble EP, Solomon DH. Alcoholism. *Ann Intern Med* 1984; **100:** 405–46.
6 Pokorny AD. How to diagnose the alcoholic. In: Messiha FS, Tyner GS, eds. *Alcoholism: a perspective.* Westbury, NJ: PJD Publications, 1980: 1–29.
7 Kearney TR, Bonime HB, Cassimatis G. The impact of alcoholism on a community general hospital. *Community Ment Health J* 1967; **3:** 373–6.
8 Moore RA. The prevalence of alcoholism in a community general hospital. *Am J Psychiatry* 1971; **128:** 638–9.
9 Barchha R, Stewart MA, Guze SB. The prevalence of alcoholism among general hospital ward patients. *Am J Psychiatry* 1968; **125:** 681–4.
10 Solomon J, Vanga N, Morgan JP, Joseph P. Emergency-room physicians' recognition of alcohol misuse. *J Stud Alcohol* 1980; **41:** 583–6.
11 Lloyd G, Chick J, Crombie E. Screening for problem drinkers among medical inpatients. *Drug Alcohol Depend* 1982; **10:** 355–9.
12 Lockhart SP, Carter YH, Staffen AM, Pang KK, McLoughlin J, Baron JH. Detecting alcohol consumption as a cause of emergency general medical admissions. *J R Soc Med* 1986; **79:** 132–6.
13 Auth JB, Warheit GJ. Estimating the prevalence of problem drinking and alcoholism in the general population: an overview of epidemiological studies. *Alcohol Hlth Res World* 1982–3; **7:** 10–21.
14 Favazza AR. Alcoholism. *Am Fam Physician* 1983; **27:** 274–8.
15 Keller M, Efron V. Alcoholism in the big cities of the United States. *J Stud Alcohol* 1956; **17:** 63–72.
16 Janis JM, Walker A. *An approach to monitoring the health status of Los Angeles County residents.* Los Angeles: UCLA, 1983: 149–64.
17 Jones DB. Initial therapy of suspected microbial corneal ulcers. II. Specific antibiotic therapy based on corneal smears. *Surv Ophthalmol* 1979; **24:** 97, 105–16.
18 Jones DB. Early diagnosis and therapy of bacterial corneal ulcers. *Int Ophthalmol Clin* 1973; **13**(4): 1–29.
19 Jones DB, Liesegang TJ, Robinson NM. Laboratory diagnosis of ocular infections. Cumitech 13, Washington, DC: American Society for Microbiology, 1981.
20 Wilkinson P, Kornaczewski A, Rankin JG, Santamaria JN. Physical disease in alcoholism. Initial survey of 1000 patients. *Med J Aust* 1971; **1:** 1217–23.

21 German E. Medical problems in chronic alcoholic men. *J Chronic Dis* 1973; **26**: 661–8.

22 Ashley MJ, Olin JS, le Riche WH, Kornaczewski A, Rankin JG. Skid row alcoholism. *Arch Intern Med* 1976; **136**: 272–8.

23 Lieber CS. *Medical disorders of alcoholism: pathogenesis and treatment.* Philadelphia: Saunders, 1982: 345–55.

24 Gomberg ES. Prevalence of alcoholism among ward patients in a Veterans Administration Hospital. *J Stud Alcohol* 1975; **36**: 1458–67.

25 Adams HG, Jordan C. Infections in the alcoholic. *Med Clin North Am* 1984; **68**(1): 179–200.

26 Liesegang TJ, Forster RK. Spectrum of microbial keratitis in South Florida. *Am J Ophthalmol* 1980; **90**: 38–47.

27 Hyndiuk RA, Nassif KF, Burd EM. Bacterial diseases. In: Smolin G, Thoft RA, eds. *The cornea. Scientific foundations and clinical practice.* Boston: Little, Brown, 1983: 147–67.

28 Mahajan VM, Alexander TA, Jain RK, Agarwal LP. Role of coagulase-negative staphylococci and micrococci in ocular disease. *J Clin Pathol* 1980; **33**: 1169–73.

29 Mahajan VM, Reddy TN, Agarwal LP. Toxigenic strains of *Staphylococcus epidermidis* and their experimental corneal pathogenicity in rabbits. *Int Ophthalmol* 1982; **5**: 155–61.

30 Jones DB. Polymicrobial keratitis. *Trans Am Ophthalmol Soc* 1981; **79**: 153–67.

31 Westermeyer T, Doheny S, Stone B. An assessment of hospital care for the alcoholic patient. *Alcoholism* 1978; **2**: 53–67.

32 Chick J, Lloyd G, Crombie E. Counselling problem drinkers in medical wards: a controlled study. *Br Med J* 1985; **290**: 965–7.

33 Paton A, Saunders JB. ABC of alcohol: definitions. *Br Med J* 1981; **283**: 1248–50.

Accepted for publication 16 December 1986.

British Journal of Ophthalmology, 1988, **72**, 160

Correspondence

Ophthalmic survey of a diabetic clinic

SIR, we read with interest the comprehensive reports by Grey *et al.*[1,2] on the ophthalmic survey of a diabetic clinic. The implications for referral policy and general eye care planning in such communities are extremely important. The authors express their satisfaction over the existing referral system,[2] and this conclusion is based on their results as shown in Table 2 of the above paper. They state that a 'lower prevalence of most forms of diabetic retinopathy was found in those patients who had not had their eyes previously examined by an ophthalmologist.'

In their results and table, however, information on the duration of the diabetes in each group has been omitted. As this information has a paramount importance and the correlation between duration of the disease and the finding of retinopathy was clearly described in the authors' previous report,[1] it is surprising that this information was not referred to in the results.

We feel that inclusion of these data might have added an additional, valuable parameter which could have changed the impression of the casual reader that patients under ophthalmologists care are more prone to exhibit diabetic retinopathy than diabetics not so examined.

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References

1 Grey RHB, Malcolm N, O'Reily D, Morris A. Ophthalmic Survey of a diabetic clinic: I. Ocular findings *Br J Ophthalmol* 1986; **70:** 797–803.
2 Grey RHB, Morris A. Ophthalmic survey of a diabetic clinic: II. *Br J Ophthalmol* 1986; **70:** 804–7.

SIR, Thank you for the opportunity to reply to the query posed by Rosenblat, David, and Yassur. The point they make regarding the prevelance of retinopathy with increasing duration of diabetes is important and is universally recognised. As they noted, the first part of our publication included information on this aspect of our findings.

In answer to their specific question Table 1 may be helpful. This information was not included in the original paper because the incidence of retinopathy was considered to be higher in the group of patients who had previously been examined by an ophthalmologist, as the presence of retinopathy was likely to be a criterion for referral. As can be seen from Table 1, the prevalence of retinopathy increases for both groups with increasing duration of disease, which is not surprising.

Table

	% Retinopathy	
Years diabetic	*Previous examination*	*No previous examination*
<5	21	14
5–	43	19
10–	54	40
15–	67	50
20+	83	52
Total	52	22

The point that we were trying to convey was that current referral practices in the population studied appeared to satisfactorily identify those with proliferative retinopathy but tended to miss a number of patients with maculopathy.

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Obituary

Herbert Fitzroy Townsend MacFetridge, DSO, TD, MA, MB, BCH, DOMS

Mr H F T MacFetridge died on 20 July 1987. Born in 1915, the son of an ophthalmic surgeon, he qualified at Trinity College, Dublin, in 1937. After house appointments in the Royal Sussex County Hospital he obtained a regular commission in the Indian Medical Service.

He served in the Western Desert as regimental medical officer to the 51st Commando and then as DADMS to the 14th Indian Field Ambulance, where he was awarded the DSO for gallantry in the field. After the war Mac trained at Birmingham Eye Hospital and Bristol Eye Hospital, during which time he was also active in the Territorial Army RAMC and was awarded the Territorial Decoration in 1962. He was appointed consultant surgeon in 1955 to the Victoria Eye Hospital in Hereford, retiring in 1979.

A past president of the Midland Ophthalmological Society and vice-president of the Hereford and Worcester St John Ambulance Brigade, he was also honoured by being made a freeman of the City of Hereford on his retirement. Though his interest lay mainly in his work, he found relaxation in reading and gardening but also played an excellent game of squash right into his 60s. His administrative skills made him a popular and outstanding chairman of the Hereford Medical Executive Committee, where he always demonstrated remarkable foresight.

He is survived by his wife Margaret, also an ophthalmologist, who always accompanied him to the various society meetings, and a son and a daughter. SM

Note

Ocular trauma conference

The First International Ocular Trauma Conference will be held on 7-22 April 1988 at Chengchow, the People's Republic of China, sponsored by the World Eye Foundation. For further information contact Donald R May, MD, Tulane University Medical School, 1430 Tulane Avenue, New Orleans, Louisiana 70112, USA.

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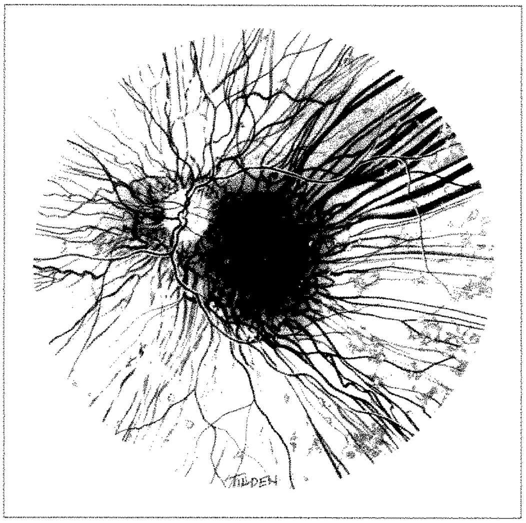

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Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

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ASTM CODEN BJOPAL 72 (2) 81–160 (1988) ISSN 0007-1161

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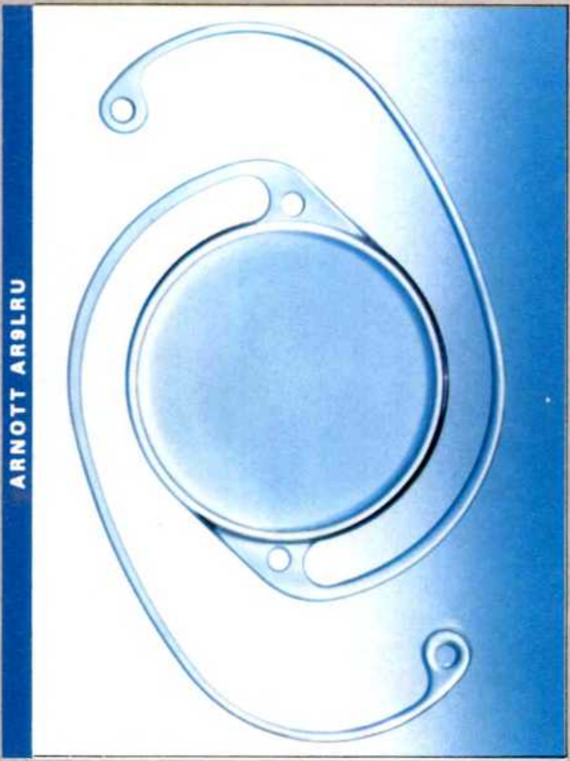

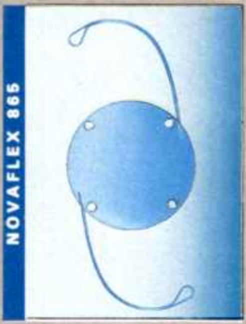

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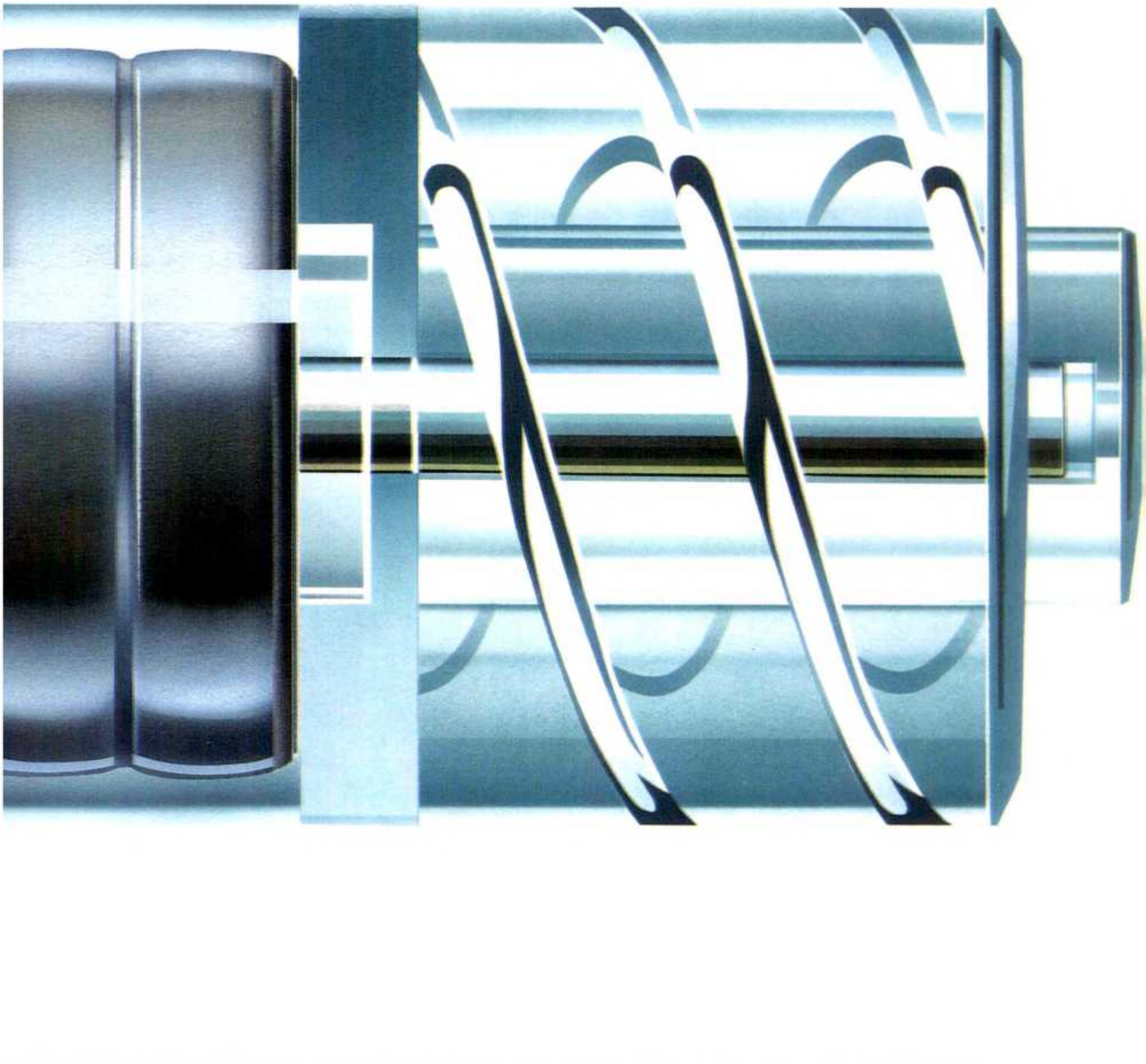

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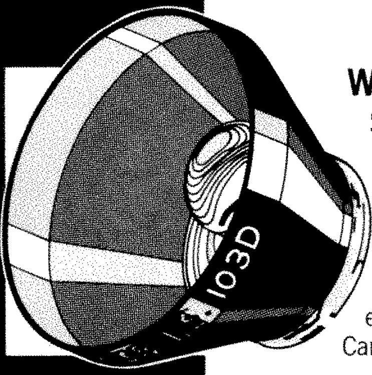

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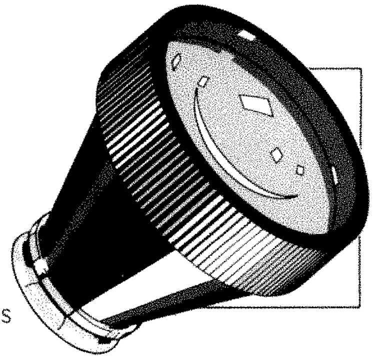

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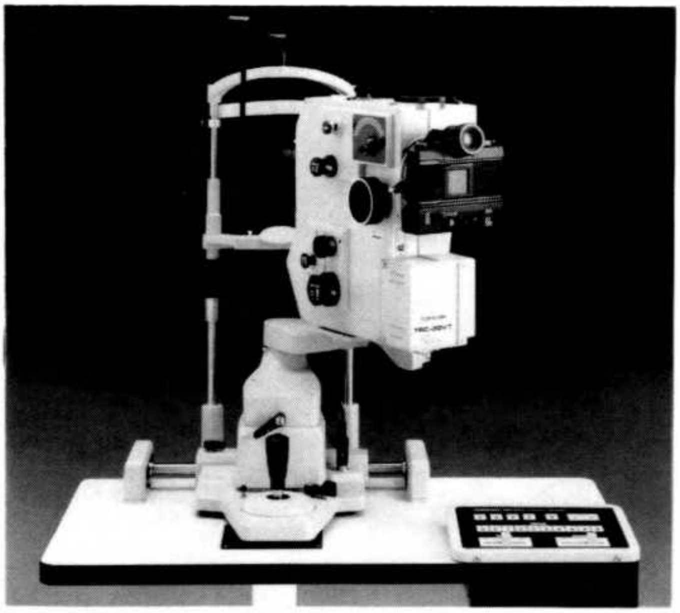

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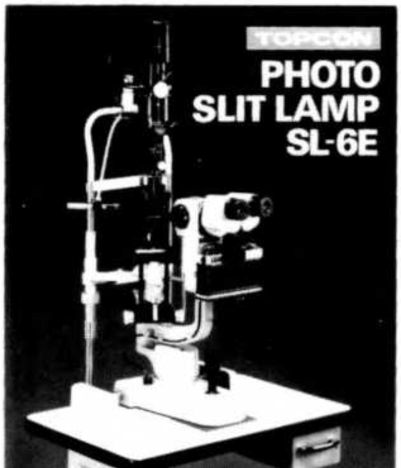

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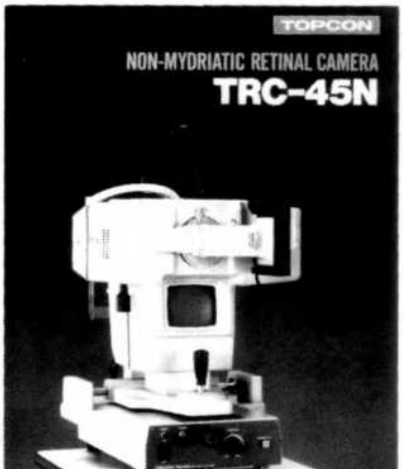

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Familial uveal melanoma

C R CANNING AND J HUNGERFORD

From Moorfields Eye Hospital, London EC1

SUMMARY The cause of uveal melanoma is unknown. In a few cases, however, factors are found in association with the disease which may play some part in the aetiology. One such factor is inheritance. Twelve families have been reported with adequate documentation during the last century in which two or more members have had uveal melanomas. At least some of these may be the result of an inherited disorder. On available data inheritance is most likely autosomal dominant with partial expressivity or incomplete penetrance. This report describes two more families each of which have two members with uveal melanomas.

The cause of most uveal melanomas is unknown. Some arise from pre-existing naevi and some are associated with neurofibromatosis and ocular or oculodermal melanocytosis.[1] Sunlight[2] and chemical carcinogens[3 4] may be oncogenic, but the data are equivocal.

Some uveal melanomas may be inherited. This report describes the case histories of two families in each of which two members had uveal melanomas—one a pair of siblings and one a mother and son. The evidence supporting a genetic basis for some uveal melanomas is discussed.

Case reports

FAMILY CASE HISTORY 1

In March 1986 a 63-year-old female presented with a three-month history of blurred vision in her left eye. She had a smooth pigmented mass in the inferonasal quadrant of that eye with a base diameter of 10 mm and a height of 7 mm. This was clinically and on ultrasound thought to be a malignant melanoma. The tumour was treated by application of a local scleral cobalt-60 plaque. There was no macroscopic evidence of extraocular spread at the time of surgery. She has remained well since.

As a result of her experience her 69-year-old brother volunteered that he had had blurred vision in his left eye for about four months. He had a melanoma in the same inferonasal location as his sister's tumour. The base diameter was 14 mm and the elevation 11·2 mm. The tumour was too large for local treatment, so the eye was enucleated. The histology was of a heavily pigmented mixed cell malignant melanoma with evidence of incipient scleral channel extension. He had no evidence of hepatic or pulmonary metastasis, though liver ultrasound showed multiple hyperechoic areas compatible with haemangiomata.

This brother and sister have nine other siblings. The family was separated at an early stage, however, so information about them is limited. Seven have died but none are thought to have had eye disease. The two live siblings are well with no ocular symptoms.

FAMILY CASE HISTORY 2

In 1962 a 33-year-old female presented with a temporal field defect in her right eye. Clinically she had a choroidal melanoma in the upper nasal quadrant. This was treated with a cobalt-60 plaque initially, then by xenon arc photocoagulation on three occasions over the next two years. In 23 years of follow-up she has remained free of local or metastatic recurrence.

Her son presented at the age of 20 years in 1976 with a left choroidal melanoma and non-rhegmatogenous retinal detachment. The eye was enucleated. Histology showed a mixed cell melanoma. A metastasis was detected on routine chest *x*-ray in the lower lobe of his left lung eight years later. This was locally resected. He has since remained well with no further overt metastatic disease.

Correspondence to C R Canning, FRCS, Moorfields Eye Hospital, City Road, London EC1V 2PD.

Discussion

Histological confirmation of melanoma was not available in two of the above patients, though a firm clinical diagnosis of melanoma was possible. There is a trend towards more conservative management of eyes with melanomas,[1] so lack of histological confirmation of the diagnosis will continue to be a factor in future reports.

A total of 12 families have been described in which two or more members had uveal melanomas.[5-16] Data from these reports are summarised in Table 1. Five families had affected siblings,[9 12 14 16] and in eight there were two or more affected generations.[5-8 10-13 15] These included two uncle/niece pairs[10 12] and two families with three affected generations.[5-7 15]

Taken together, no clear mode of inheritance has emerged. Lynch[12] proposed an autosomal dominant inheritance in some of these families. The pattern of inheritance may be obscured by incomplete gene penetrance and because some patients genetically predisposed to uveal melanoma may die of unrelated disease before the tumour is apparent.

There are 18 females and eight males in this group of familial cases. The sex distribution is not significantly different from that of a large series of non-familial cases reported by Jensen.[17]

There is reason to suspect that some uveal melanomas may be inherited. Familial tumours tend to occur at an earlier age than the same tumour occurring sporadically.[12] The mean age at which uveal melanoma was diagnosed in the reported families, including the four patients described above, is 42·2 years (SD 15·1 years). By comparison, Jensen's series[17] of 292 patients with non-familial uveal melanomas in Denmark had a mean age at diagnosis of 56·4 years (SD 13·7 years). The difference between the means is statistically significant.

Some skin melanomas are inherited.[18 20] The dysplastic naevus syndrome is inherited as an autosomal dominant disorder. It increases the risk of developing skin melanoma a hundred-fold and may account for up to 40% of all skin melanomas.[21] Given the common embryological original uveal and skin melanocytes, it is reasonable to postulate that an inherited uveal naevus syndrome might exist as a precursor for some uveal melanomas. Rodriguez-Sains[22] has shown that uveal, iris, and conjunctival naevi all occur more commonly in patients with dysplastic naevus syndrome, though there is no proof that uveal melanomas are more frequent.[18] Nevertheless, skin and uveal primary melanomas have been described together in the same patients, some

Table 1 *Details from reports on familial uveal melanomas*

Author	*Case: relation*	*Sex*	*Year of diagnosis*	*Age at diagnosis*	*Eye*	*Outcome*
Davenport[5]	Proband	F	1871	33	L	Died after 7 mth
Silcock[6]	Daughter	F	1899	19	L	Died after 5 yr
Parsons[7]	Daughter	F	1904	38	L	Died after 1 yr
	Grand-daughter	F	1918	29	L	Died after 4 yr
	Grand-daughter	F	1914	19	?	Alive at 10 yr
Gutmann[8]	Proband	F	1891	32	R	Alive at 4 yr
	Father	M	?	?	R	Died 1889
Pfingst and Graves[9]	Proband	M	1919	44	L	Alive at 3 yr
	Brother	M	1921	47	L	Alive
Waardenberg[10]	Proband	F	1925	19	L	Died with metastases
	Uncle	M	1940	?	R	No follow-up
Bowen, *et al.*[11]	Proband	F	1953	45	R	Died at 1 yr
	Daughter	F	1963	26	L	Alive at 6 mth
Lynch, *et al.*[12]	Proband	M	1964	59	R	Died at 2 yr
	Sister	F	1963	56	R	Alive at 3 yr
	Proband	F	1962	33	L	Died at 1 yr
	Uncle	M	?	?	R	Died age 57 yr
Tasman[13]	Proband	F	?	58	R	No follow-up
	Daughter	F	1967	38	R	No follow-up
Green, *et al.*[14]	Proband	M	1976	50	L	No follow-up
	Father	M	1926	46	R	Died at 7 yr
Walker, *et al.*[15]	Proband	M	1976	67	L	Alive at 3 yr
	Father	M	1926	44	L	Died at 7 yr
	Grand-mother	F	?	?	?	No follow-up
Simons, *et al.*[16]	Proband	M	1974	50	L	Alive at 5 yr
	Sister	F	1981	56	R	Alive at 2 yr
Canning and Hungerford	Proband	F	1986	63	L	Alive at 6 mth
	Brother	M	1986	67	L	Aliver at 4 mth
	Proband	F	1962	33	L	Alive at 20 yr
	Son	M	1976	20	L	Alive at 4 yr

of whom have also had the dysplastic naevus syndrome.[19 20 23-25]

Uveal melanoma is an uncommon condition with an incidence of between 4 and 10 per 100 000 per year in Caucasian populations.[26] Shammas and Watzke[27] estimated the cumulative lifetime risk of developing a uveal melanoma to be one in 2500 and the risk of one individual getting two primary uveal melanomas by chance alone to be one in 50 million.

The probability of two tumours occurring by chance alone in members of the same family is more difficult to estimate. It is necessary to know the size of the family. This will vary both in absolute numbers and in the accuracy of patient recall of family history. The probability should, however, be low. That there have been only 14 families with uveal melanomas reported in the last century suggests that the condition is indeed uncommon, though it is probably underdiagnosed and reported through lack of awareness of the importance of the family history.

The chance of three or more family members having sporadic uveal melanomas becomes exceedingly small. In a case history such as that reported by Davenport,[5] Silcock,[6] and Parsons,[7] where five members were affected in three generations, some factor other than chance has to be involved.

No genetic markers have yet been identified in these patients, and recent advances in chromosomal analysis may usefully be applied here. Meanwhile, family history should receive greater attention in the management of uveal melanomas.

References

1 Shields JA. *Diagnosis and management of intraocular tumors*. St Louis: Mosby, 1983.

2 Tucker MA, Shields JA, Hartge P, *et al.*. Sunlight exposure as a risk factor for intraocular malignant melanoma. *N Engl J Med* 1985; **313:** 789–92.

3 Albert DM, Puliafito CA, Fulton AB, *et al.* Increased incidence of choroidal malignant melanoma occurring in a single population of chemical workers. *Am J Ophthalmol* 1980; **89:** 323–37.

4 Louria DB, Coumbis RJ, Avenhar MA. An apparent small cluster of choroidal melanoma cases. *Am J Ophthalmol* 1982; **94:** 172–80.

5 Davenport RC. Family history of choroidal sarcoma. *Br J Ophthalmol* 1927; **11:** 443–5.

6 Silcock AQ. Hereditary sarcoma of the eyeball. *Trans Pathol Soc Lond* 1892; **43:** 140–1.

7 Parsons JH. Some anomalous sarcomata of the choroid. Case 4. *Trans Ophthalmol Soc UK* 1905; **25:** 205–11.

8 Gutmann G. Casuistischer beitrag zur Lehre von den Geschwulsten des Augafels. *Arch Augenheilkd* 1985; **31:** 158–80.

9 Pfingst AO, Graves S. Melanosarcoma of the choroid occurring in two brothers. *Arch Ophthalmol* 1921; **50:** 431–9.

10 Waardenburg PJ. Melanosarcoma van bet vog bij verschillende leden eener zelfde familie. *Ned Tijdschr Geneeskd* 1940; **84:** 4718–9.

11 Bowen SF, Brady H, Jones VL. Malignant melanoma of the eye occurring in two successive generations. *Arch Ophthalmol* 1964; **71:** 805–6.

12 Lynch HT, Anderson DE, Krush AJ. Heredity and intraocular melanomas. *Cancer* 1968; **21:** 119–25.

13 Tasman W. Familial intraocular melanoma. *Ophthalmology* 1970; **74:** 955–8.

14 Green GJ, Hong WK, Everett JR, *et al.*. Familial intraocular malignant melanoma. A case report. *Cancer* 1978; **41:** 2481–3.

15 Walker JP, Weiter JJ, Albert DM, *et al.*. Uveal malignant melanoma in three generations of the same family. *Am J Ophthalmol* 1979; **88:** 723–6.

16 Simons KB, Hale LM, Morrison HM. Choroidal malignant melanoma siblings. *Am J Ophthalmol* 1983; **96:** 675–80.

17 Jensen OA. Malignant melanoma of the human choroid. Recent follow up of cases in Denmark 1943–1952. *Acta Ophthalmol (Kbh)* 1970; **48:** 1113–28.

18 Greene MH, Sanders RJ, Chu FC. The familial occurrence of cutaneous melanoma, intraocular melanoma and the dysplastic nevus syndrome. *Am J Ophthalmol* 1983; **96:** 238–45.

19 Abramson DH, Rodriguez-Sains RS, Rubman R. B-K mole syndrome. Cutaneous and ocular melanoma. *Arch Ophthalmol* 1980; **98:** 1397–9.

20 Oosterhuis JA, Went LN, Lynch HT. Primary choroidal and cutaneous melanomas, bilateral choroid melanomas, and familial occurrence of melanomas. *Br J Ophthalmol* 1982; **66:** 230–3.

21 Taylor MR, Guerry D IV, Bondi EE, *et al.* Lack of association between intraocular melanoma and cutaneous dysplastic nevi. *Am J Ophthalmol* 1984; **98:** 478–82.

22 Rodriguez-Sains RS. Ocular findings in patients with dysplastic nevus syndrome. *Ophthalmology* 1986; **93:** 661–5.

23 Bellet RE, Shields JA, Soll DB, Bernardino EA. Primary choroidal and cutaneous melanomas occurring in a patient with the B-K mole syndrome phenotype. *Am J Ophthalmol* 1980; **89:** 567–70.

24 Paton D, Thomas LB. Simultaneous occurrence of primary malignant melanomas of the eye and skin. *Arch Ophthalmol* 1959; **62:** 645–52.

25 Augsberger JJ, Shields JA, Frank PE, Mastrangelo MJ. Diffuse primary malignant melanoma after prior primary cutaneous malignant melanoma. *Arch Ophthalmol* 1980; **98:** 1261–4.

26 Reese A. *Tumors of the eye*. 3rd ed. Hagerstown: Harper and Row, 1976: 177–8.

27 Shammas HF, Watzke RC. Bilateral choroidal melanomas. *Arch Ophthalmol* 1977; **95:** 617–23.

Accepted for publication 7 January 1987.

British Journal of Ophthalmology, 1988, **72**, 244–245

Two cases of primary bilateral malignant melanoma of the choroid

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SUMMARY The first two Swedish cases of primary bilateral malignant melanoma of the choroid are presented. In one case bilateral histological confirmation was obtained as both eyes were enucleated. In the other case one eye was enucleated and the other irradiated with an episcleral ruthenium plaque. Sweden has a population of 8·38 millions, so that bilateral choroidal melanomas may be less rare than previously thought.

The annual incidence of unilateral malignant melanoma of the choroid is 5–7·5 per million Caucasians. It is much less frequent in a non-Caucasian population. Bilateral choroidal malignant melanoma is consequently believed to be extremely uncommon. It has been estimated to occur once every 18 years in the United States.[1] A few cases world-wide have been described,[2-6] some of them associated with other primary malignancies.[7 8] In some other cases metastases from a cutaneous melanoma simulated bilateral primary lesions.[9]

We present two cases of primary bilateral malignant melanoma of the choroid, presumably the first two Swedish cases reported.

Case reports

CASE 1

A 72-year-old woman had had blurring of vision in the right eye for the past week. The physician admitting her to hospital noted a choroidal mass in the lower half of her right eye extending from the equator to the macula. There was a similar but smaller lesion in the lower temporal quadrant of her left eye located somewhat more anteriorly.

The visual acuity was hand movements in the right eye and 20/20 in the left eye. Diascleral transillumination proved negative in the right eye but positive in the left eye. Echography and fluorescein angiography demonstrated findings suggestive of malignant melanoma in both eyes.

She was otherwise in good health, and orbital CT scan, liver scan, abdominal ultrasound, bone scan, and chest *x*-ray failed to reveal anything abnormal.

Owing to extensive tumour growth the right eye was enucleated in March 1980. Pathological examination of the eye showed a pigmented tumour 9×9×11 mm in size mainly composed of epithelioid cells. Tumour growth was noted in the deeper parts of the sclera and Bruch's membrane was ruptured. There was no extrascleral extension. The left eye was irradiated in July with an episcleral plaque of ruthenium-106, and the tumour promptly regressed.

After a cataract extraction in March 1985 the patient has retained a visual acuity of 20/30. She is still in good health with no signs of systemic illness.

CASE 2

An 86-year-old man was first examined by an ophthalmologist in May 1975 when he complained of blurred vision in both eyes. Visual acuities were noted to be 20/40 in the right eye and 20/200 in the left eye. The visual disturbance was due to yellow spots, presumed to be degenerative changes, in both macular regions. In November the patient reappeared with deteriorated visual acuity, namely hand movements in the right and 20/200 in the left eye. The yellowish lesions now appeared solid and slightly protruding; the right eye had an associated retinal detachment.

The patient's history included previous surgery for a carcinoma of the rectum. No treatment was

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given, as the protruding growths were regarded as metastases.

Four months later the patient presented with severe pain in his right eye. A high intraocular pressure not responding to therapy was noticed, and, as only perception of light remained, the eye was enucleated.

Nothing was heard of him until 1980, when he reappeared with pain in the remaining left eye due to raised intraocular pressure. The visual acuity was reduced to perception of light, and the eye had to be enucleated.

Both enucleated eyes were histopathologically examined. The right eye contained a choroidal malignant melanoma 9×9×9 mm in size. The tumour was composed of spindle B cells and penetrated Bruch's membrane, but there was no extrascleral extension. His left eye showed a similar spindle cell melanoma 12×10×10 mm in size. Here also Bruch's membrane was ruptured. The tumour infiltrated the sclera but did not grow extrasclerally.

There was no search for extraocular metastases, but the patient is still in remarkably good health, without clinical signs suggesting metastatic disease. He is now 97 years old.

Discussion

The first case report illustrates the current trend in Sweden to treat choroidal melanomas in a conservative manner. Episcleral plaques containing ruthenium-106 have been used in Sweden since 1979 to treat medium sized choroidal melanomas. In such cases there is no histological confirmation of the diagnosis unless treatment fails and the eye is enucleated. However, in the first case the clinical appearance was undoubtedly that of a choroidal melanoma, and this was substantiated by ultrasonography and fluorescein angiography. Furthermore, the tumour responded promptly to irradiation therapy.

In the second case both eyes were enucleated, and consequently we obtained bilateral histological confirmation. It is interesting to note that metastatic spread has not occurred, despite enucleation in a late stage.

As noted above, bilateral malignant melanoma of the choroid is rare. The population of Sweden is 8·38 millions, so that bilateral tumours may occur somewhat more often than previously thought.

References

1 Schammas HF, Watzke RC. Bilateral choroidal melanomas. *Arch Ophthalmol* 1977; **95:** 617–23.
2 Shine FW. Report of a case of bilateral sarcoma of the uveal tract. *Clin Rep NY Eye Ear Infirm* 1930; **1:** 31–3.
3 Lau T. Das primär doppelseitige maligne Melanom der Choroidea. *Klin Monatsbl Augenheilkd* 1981; **179:** 333–5.
4 Oosterhuis JA. Primary choroidal and cutaneous melanomas, bilateral choroidal melanomas, and familial occurrence of melanomas. *Br J Ophthalmol* 1982; **66:** 230–3.
5 Ide CH, Ford T, Oxenhandler RW, Havey A, Adelstein EH. Gleichzeitiges bilaterales malignes Melanom der Choroidea ohne ursprünglichen Nachwis von Metastasen. *Fortschr Ophthalmol* 1983; **80:** 304–8.
6 Migdal C, MacFarlane A. Bilateral primary choroidal melanoma. *Br J Ophthalmol* 1984; **68:** 268–71.
7 Tsukahara S, Wakui K, Ohzeki S. Simultaneous bilateral primary diffuse malignant uveal melanoma: case report with pathological examination. *Br J Ophthalmol* 1986; **70:** 33–8.
8 Mullaney J, Mooney D, O'Connor M, McDonald GSA. Bilateral ovarian carcinoma with bilateral uveal melanoma. *Br J Ophthalmol* 1984; **68:** 261–7.
9 de Bustros S, Augsburger JJ, Shields JA, Shakin EP, Pryor CC. Intraocular metastases from cutaneous malignant melanoma. *Arch Ophthalmol* 1985; **103:** 937–40.

Accepted for publication 26 June 1987.

British Journal of Ophthalmology, 1988, **72**, 246–247

Intracerebral metastases from ocular melanoma

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SUMMARY A blind painful eye may harbour an unsuspected malignant melanoma. We report a case of ocular melanoma that presented with confusion owing to direct extension via the optic nerve into the anterior cranial fossa.

Case report

A 71-year-old woman was admitted through casualty too confused to give a history. From friends it was learned that she had been suffering from headaches for several months. Her left eye had apparently been damaged in a road accident in 1969. Three months previously she was seen at another hospital complaining of pain and watering of her left eye. After that visit her name was placed on a waiting list for enucleation of the eye.

On examination at this hospital she was unkempt, dehydrated, and mildly pyrexial (37·7°C). There was no lymphadenopathy, the chest was clear, and there were no abdominal masses. She was disorientated in time and space. No neck stiffness was present, but she had bilateral extensor plantar responses.

Examination of the eyes revealed visual acuities of counting fingers only on the right with no perception of light on the left. The right pupil reacted sluggishly to light and the right disc was pale. The left eye was injected, the cornea was blood stained, and the anterior chamber flat. New vessels were evident on the left iris superiorly, with hyphaema preventing a view of the fundus. The left intraocular pressure was grossly elevated.

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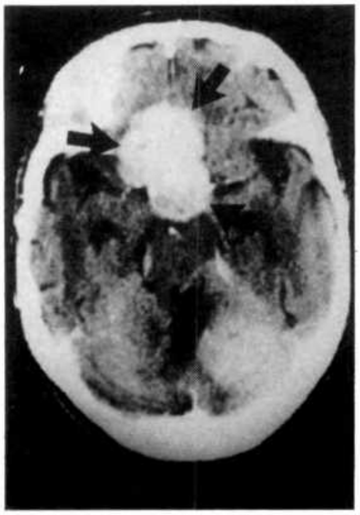

Fig. 1 *Contrast-enhanced CT head scan showing a left sided lobulated mass in the subfrontal region (arrowed).*

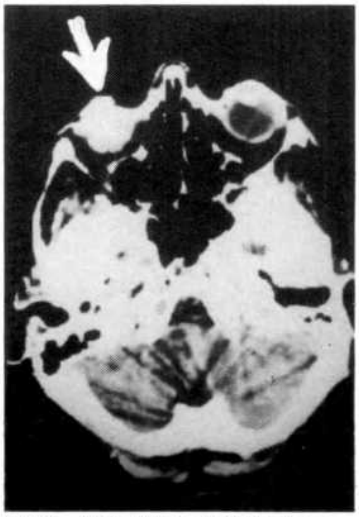

Fig. 2 *Non-enhanced CT head scan showing calcified left globe (arrowed).*

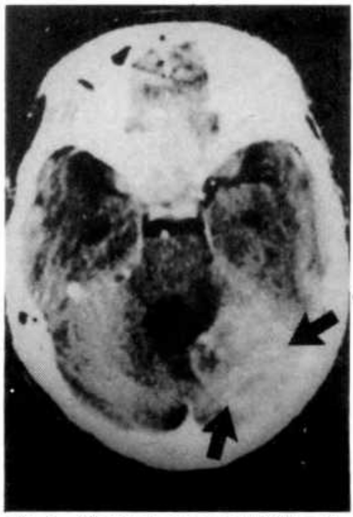

Fig. 3 *Contrast-enhanced CT head scan showing mass in right posterior fossa producing compression of the brain stem (arrowed).*

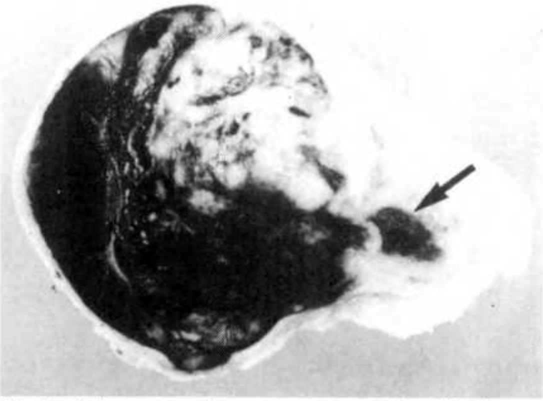

Fig. 4 *Left eye cut to show necrotic tumour invading the optic nerve (arrowed).*

Chest *x*-ray, routine haematological and biochemical tests, including liver function tests, were normal. Computed tomography of the orbits and brain showed a lobulated enhancing mass involving the left subfrontal region, suprasellar cistern, medial temporal lobe, and third ventricle (Fig. 1). The left optic nerve was thickened with widening of the optic canal. The globe appeared calcified, with a dense vitreous (Fig. 2). A second lesion appeared to arise on the inferior surface of the right side of the tentorium and lateral wall of the posterior fossa (Fig. 3). This was causing oedema in the adjacent cerebellar hemisphere producing compression of the brain stem.

Neurosurgical intervention was considered too hazardous, and she was treated with oral dexamethasone. Her condition deteriorated and she died 18 days after admission.

PATHOLOGY

At necropsy the cause of death was found to be fresh thrombus in both pulmonary arteries. In the cranium a necrotic tumour bulged from the floor of the third ventricle extending anteriorly along the left optic nerve. The optic chiasm was displaced to the right, and tumour was infiltrating the adjacent left temporal lobe. The left eye and optic nerve were infiltrated by tumour. Necrotic tumour was also present in the right cerebellar hemisphere.

Microscopy of these tumours and the left eye showed malignant melanoma of epithelioid pattern. Much of the tumour was necrotic, but areas of viable mitotically active tumour cells had survived. The tumour had infiltrated the sclera of the left eye and spread along the optic nerve into the cranial cavity (Fig. 4). There was no macroscopic evidence of metastasis outside the brain.

Discussion

Optic nerve invasion by ocular melanoma is uncommon, being noted in 0·6% of 2535 cases.[1] Intracranial invasion via the optic nerve is rare. Terry documented two cases of histologically proved optic nerve spread in which presumed chiasmal involvement led to a hemianopia in the fellow eye.[2] To our knowledge there have been no clinicopathological reports of intracranial invasion by ocular melanoma without evidence of other extracranial metastasis at necropsy.

The presentation of metastasis from ocular melanoma is usually with symptoms referable to the liver or lungs.[3] In a report of necropsies performed on patients with ocular melanoma, metastases were found in the liver in every case in which metastatic lesions were present.[4]

This case illustrates the need to maintain an index of suspicion about the underlying cause of blind, painful eyes and emphasises the value of CT scanning of the head and orbits in these patients.

We thank Professor I R Cameron for permission to report this case, Professor J R Tighe for performing the necropsy, and Richard Dewhirst for preparation of the illustrations.

References

1 Wilder HC, Paul EV. Malignant melanoma of the choroid and ciliary body. A study of 2535 cases. *Milit Surg* 1951; **109:** 370–8.
2 Terry TL. Malignant melanoma—so-called sarcoma—of uvea. *Arch Ophthalmol* 1940; **24:** 206–14.
3 Shields JA. Current approaches to the diagnosis and management of choroidal melanomas. *Surv Ophthalmol* 1977; **21:** 443–63.
4 Zakka KA, Foos RY, Omphroy CA, Straatsma BR. Malignant melanoma: analysis of an autopsy population. *Ophthalmology* 1980; **87:** 549–56.

Accepted for publication 29 January 1987.

British Journal of Ophthalmology, 1988, 72, 248–252

Bilateral ocular disease as the initial presentation of malignant lymphoma

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SUMMARY Malignant lymphocytic lymphoma rarely involves the eye. In two patients we found ocular signs and symptoms as the initial presentation of systemic disease. In the first patient periorbital swelling and ptosis of one year's duration ultimately proved to be the result of malignant lymphoma. After resolution of swelling and ptosis with chemotherapy, the patient returned with diffuse iris involvement and uveitis with a hypopyon. In the second patient an acute change of refractive error proved to be the result of a lymphomatous deposit in the choroid. In both instances common symptoms were the initial manifestations of a diffuse malignant disease.

Although malignant lymphocytic lymphoma involves the orbit in 2–3% of cases, intraocular lesions are very uncommon. In any event infiltration of ocular or orbital tissues is usually a late manifestation of the disease. We describe here two patients with ocular and adnexal involvement by malignant lymphocytic lymphoma in whom these ocular signs were the first indication of systemic disease. For this reason the ophthalmologist must be aware of the varied presentations of malignant lymphoma in the eye and orbit.

Case reports

CASE 1

A 60-year-old white woman first noted swelling round her right eye in September 1982. The painless periorbital swelling persisted and became bilateral. In January 1983 an ophthalmologist treated her with topical steroids and antibiotics, but there was no improvement. In the same month she was admitted to the hospital for further medical evaluation. At that time she denied any history of fevers, muscle aches, pain, or rashes. Her past medical history was remarkable only for arthritis and for a radical mastectomy in 1982 for breast carcinoma without subsequent radiotherapy or chemotherapy.

A general physical examination showed an enlarged right submandibular lymph node, but she showed no cervical or supraclavicular adenopathy or hepatosplenomegaly. Her visual acuity was 20/40 OD, 20/70 OS. She had bilateral periorbital swelling with secondary ptosis. The palpebral conjunctiva was puffy and reddened, with redundant folds. The results of ocular examination were within normal limits.

A CT scan of the head showed a density in the right maxillary antrum without evidence of bony destruction. Although no note was made of any orbital lesions, a subsequent review of the CT scan revealed a subtle diffuse infiltration of the orbit. Exploration of the sinus was performed through a Caldwell-Luc incision, and a large cyst was removed from the maxillary sinus. Biopsy of the palpable submandibular lymph node was done at the same time. Microscopic study of the antral cyst revealed only the non-specific inflammation of the sinus mucosa. The lymph node changes were interpreted as fibrotic reactive hyperplasia. It was believed that a tumour, cardiovascular disease, and vasculitis had been ruled out, and that the periorbital swelling was non-specific, possibly secondary to Graves' disease or amyloid, although all thyroid tests were normal. She was discharged on hydroxyzine hydrochloride tablets, and was to be followed up by her ophthalmologist.

The periorbital swelling persisted and progressed, so that she soon noticed proptosis and diplopia. On 19 September 1983 the patient came to the Scheie

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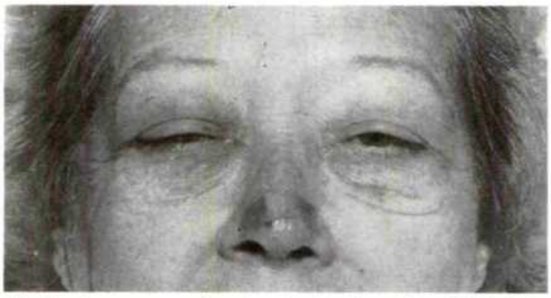


Fig. 1 *Appearance of patient 1 at the time of her initial visit. Note ptosis and periorbital swelling.*

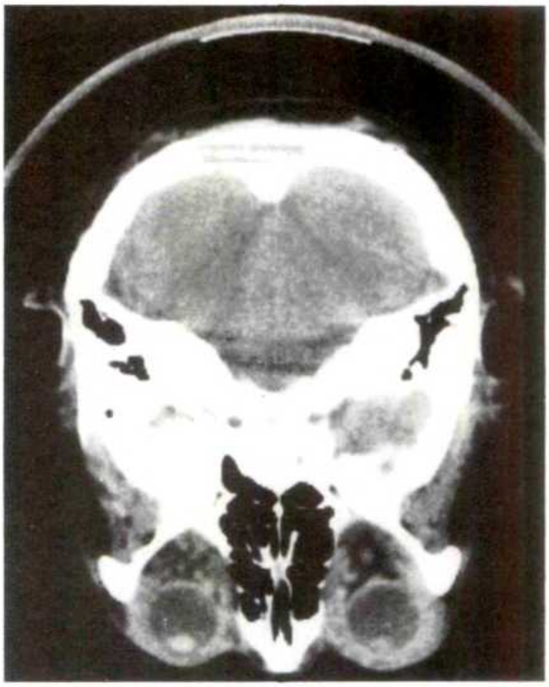


Fig. 3 *Axial view of the orbit shows diffuse infiltration of lymphoma throughout the orbit.*

Eye Institute. Ophthalmic examination revealed visual acuity to be 20/80 OU with symmetrical periorbital soft tissue swelling, exophthalmos, and restricted extraocular movements (Fig. 1). Abnormal tissue densities were palpable beneath the skin of the lids bilaterally. Fundus examination revealed choroidal folds (Fig. 2). Ultrasound examination showed low reflective, regularly structured, multilobulated lesions involving orbital soft tissues, lid, extraocular muscles, and lacrimal glands. A general medical examination showed nothing abnormal. The patient had no lymphadenopathy or enlargement of liver or spleen. CT scan at this time showed extensive infiltration of both orbits by soft tissue masses of various sizes (Fig. 3). A biopsy of the nodular tissue by anterior orbitotomy revealed a fibrous, salmon coloured tissue which on histological section was composed of poorly differentiated lymphoblasts (Fig. 4). Further staging by oncologists demonstrated splenic enlargement on abdominal CT scan and bone marrow involvement consistent with poorly differentiated lymphocytic lymphoma. As the patient denied fever, night sweats, or weight loss, she was staged IV A. Chemotherapy was begun on 30 September with cyclophosphamide 750 mg/m^2 by mouth, doxorubicin hydrochloride 50 mg/m^2, vincristine 1·5 mg/m^2, and prednisone 100 mg. The cyclophosphamide, doxorubicin, and vincristine were given on day 1. Prednisone was given on five consecutive days following initiation of therapy. This regimen was repeated approximately every three weeks. By 12 October the patient showed dramatic improvement, with resolution of periorbital swelling and diplopia (Fig. 5). Subsequently she was given six additional treatments over five months, with continued improvement in her condition.

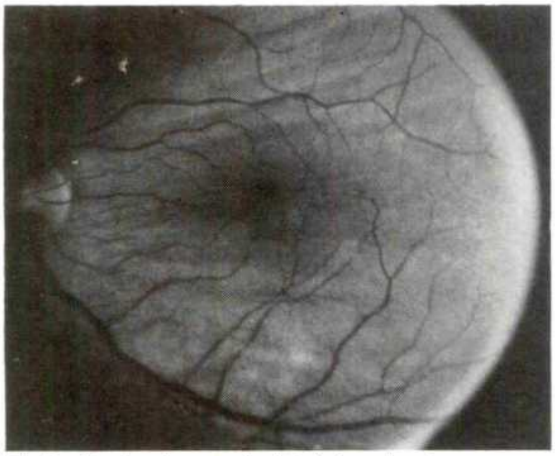


Fig. 2 *Fundus photograph of the left eye showing chorioretinal folds secondary to infiltration of lymphomatous lesions.*

In January 1985 the patient first noted sharp pain, redness, and intermittent blurred vision in her left eye. She had received her last chemotherapeutic treatment in October 1983 and had been asymptomatic since that time. On examination at the initial visit in January 1985 her visual acuity was 6/12 OU. She showed no signs of exophthalmos, decreased extraocular movements, or periorbital swelling. On slit-lamp examination there was corneal epithelial oedema, 2+ anterior chamber cells, and flare with a few fine keratitic precipitates in her left eye. Her intraocular pressures were 11 mmHg in OD and 34

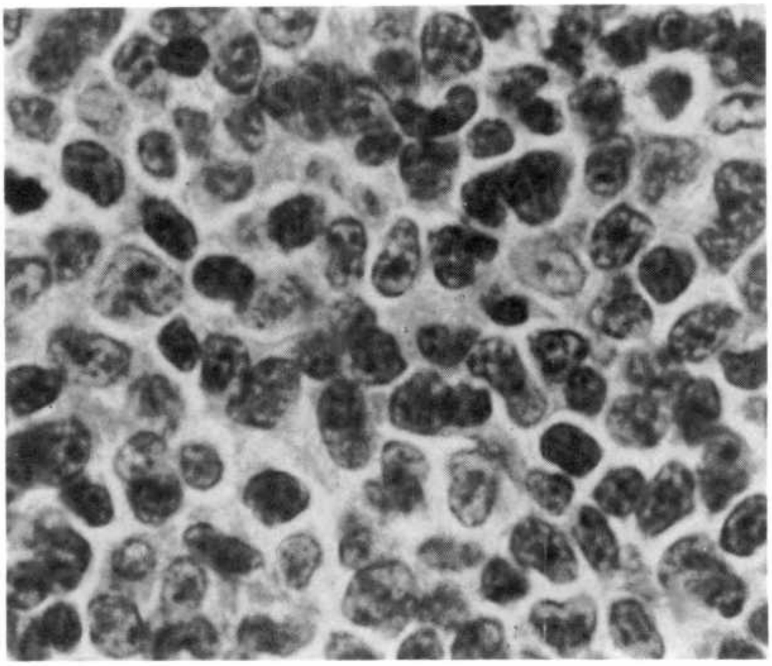


Fig. 4 *Cells of malignant lymphoid infiltrate have large vesicular, cleaved or reniform nuclei and prominent nucleoli. H and E, ×400.*

mmHg in OS, with open angles in both eyes. Her fundus examination was normal. She was started on prednisolone sodium phosphate solution in the left eye four times a day.

On repeat examination a week later she no longer noted the pain and redness. Her physical signs had resolved, and the steroids were gradually tapered. Over the next several months she had two episodes of uveitis which responded to steroids and cycloplegia. In June 1985 the uveitis again returned, but this time it did not respond to treatment. The oncologist who had been following her up found recurrent lymphoma of the abdomen and chest. By 17 July 1985 her vision had dropped to 20/80, with a large hypopyon and 4+ cell and flare with dramatic nodular iris infiltrates (Fig. 6). The patient was put on chemotherapy with N-methylfermanide, but without improvement of her uveitis or systemic lymphoma. Treatment with 2400 rads of radiation therapy did not help. Another biopsy was done in the hope of obtaining a more accurate diagnosis for treatment. Histological sections of a subcutaneous nodule in the right leg showed a diffuse, undifferentiated (non-Burkitt) cell type by the Rappaport classification. Since that time the patient's vision has dropped to light perception OS and remains 6/6 OD. The uveitis persists despite several additional treatments with chemotherapy.

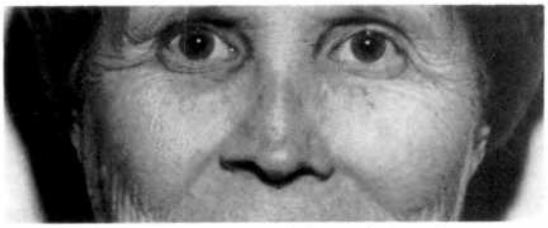


Fig 5 *After two treatments with chemotherapy the patient shows resolution of her periorbital swelling and ptosis.*

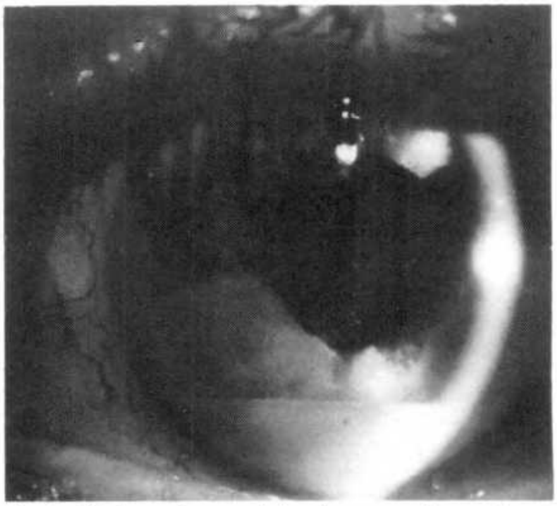


Fig. 6 *Slit-lamp photograph showing an anterior uveitis and hypopyon, with a diffuse iris infiltration.*

CASE 2

A 55-year-old white male first noted blurred vision in his left eye which improved when he removed his myopic correction. He was seen by an ophthalmologist, who noted a serous detachment of the left macula overlying a solid, pale white choroidal mass which accounted for the change in his refraction. In addition the physician noted an elevated, amelanotic lesion over the vortex vein in the superotemporal periphery of the same eye. Although the patient had no other systemic symptoms, it was decided to send him for a further examination to rule out metastatic disease.

On 16 April 1984 the patient was admitted to the Hospital of the University of Pennsylvania for investigation of oesophageal lesions seen on radiography of the upper gastrointestinal tract. At that time he was referred to the Ophthalmology Service. He noted no change in his symptoms. We found his visual acuity was 6/6 OU with a refractive error of $-4{\cdot}00 + 0{\cdot}75 \times 180$ OD and $+1{\cdot}00$ sphere OS. In the left eye the previously noted macular and peripheral lesions were unchanged. However, during the examination we noted for the first time, a 3 mm elevated pale white choroidal lesion overlying the vortex vein in the right eye. The remainder of the ocular examination was normal. On fluorescein angiogram the three lesions hyperfluoresced early and stained late (as shown in Fig. 7). There was some leakage from the foveal lesion in the left eye. The angiogram was interpreted as compatible with metastatic disease.

Biopsy of the oesophageal lesions by endoscopy revealed a mixed lymphocytic lymphoma with small and large cells. Further examination ultimately revealed diffuse involvement of the oesophagus, bone marrow, and submental, cervical, and retroperitoneal lymph nodes, so the disease was staged as grade 4. Chemotherapy was initiated with vincristine, cyclophosphamide, and dexamethasone.

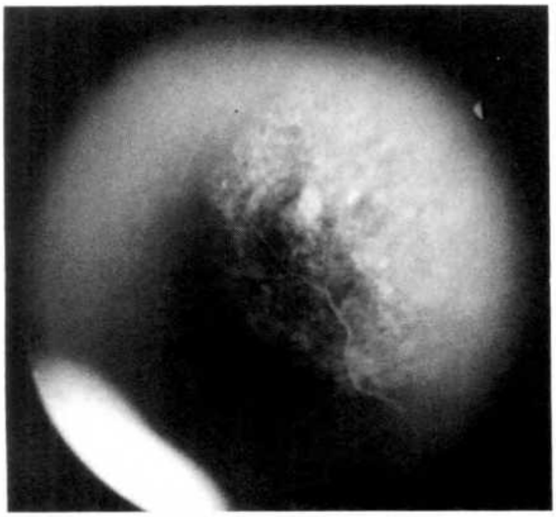


Fig. 7 *Fluorescein angiogram of the left eye showing early hyperfluorescence of superotemporal lesion.*

By 10 May 1984 the refractive error in the left eye had reverted to its pre-existing state, with resolution of the serous detachment. The two peripheral lesions noted in the superotemporal quadrants in both eyes had also regressed, leaving only a scattered pigment epithelial reaction over the previous areas of involvement. Similarly, the oesophageal and lymph node lesions cleared after seven courses of chemotherapy.

Discussion

This report concerns two patients with diffuse lymphocytic lymphoma whose initial symptoms led them to consult an ophthalmologist. The first patient presented with chronic periorbital swelling and ptosis (which had been increasing) for one year. Subsequently the patient returned with diffuse iris infiltration and uveitis which initially responded to steroids, and then progressed despite radiation therapy and several courses of chemotherapy. In the second patient a change in refraction secondary to lymphomatous choroidal deposits brought him to an ophthalmologist, who initiated the examination that led to the diagnosis of a malignant lymphocytic lymphoma. Neither patient noted night sweats, fever, weight loss, or any other systemic manifestations of the disease.

Orbital infiltrates are not uncommon in malignant lymphoma, occurring in 2–4% of patients, but it is usually a late complication and may be difficult to diagnose.[1-3] The conjunctiva is the most frequent tissue involved followed by the lid, orbit, and lacrimal gland. Most lesions occur unilaterally, involving right and left sides equally frequently. Periorbital swelling is the commonest presenting symptom followed by proptosis, ptosis, pain, and poor or blurred vision. Abnormal tissue can be palpated in over 90% of orbital metastases. Most lesions are present for 8 to 10 months prior to diagnosis.[4]

In contrast, intraocular involvement in lymphoma is uncommon, except in cases of reticulum cell sarcoma or large cell histiocytic lymphoma. Reticulum cell sarcoma usually presents as a chronic uveitis which is not responsive to steroids in a patient in the sixth or seventh decade of life.[5-7] Reticulum cell sarcoma may also present with choroidal or retinal lesions.[6,7] Multiple pigment epithelial detachments are considered characteristic of this disease.[8] The uveitis responds to radiation therapy.[9]

Intraocular infiltration is especially rare in patients with lymphocytic lymphoma. A literature review reveals only isolated case reports. One patient with lymphoblastic lymphoma was noted to have a perivenous retinal infiltrate, associated with haemorrhages, venous congestion, and cotton-wool patches.[10] There are two reports of choroidal infiltration in lymphocytic lymphoma. Hartshorne described a 3-year-old child with lymphosarcoma of the choroid.[11] Chambers and Mosher reported on a 47-year-old Caucasian man with generalised lymphoblastic lymphoma without clinical signs of intraocular involvement. Necropsy revealed microscopic infiltration of the choroid in the posterior pole.[12]

In the first patient the intraocular involvement was seen late in the course of the disease and initially responded well to topical steroids. Subsequently the uveitis recurred and did not respond to steroids, chemotherapy, or radiation therapy. In the second patient the choroidal lesions responded well to systemic chemotherapy.

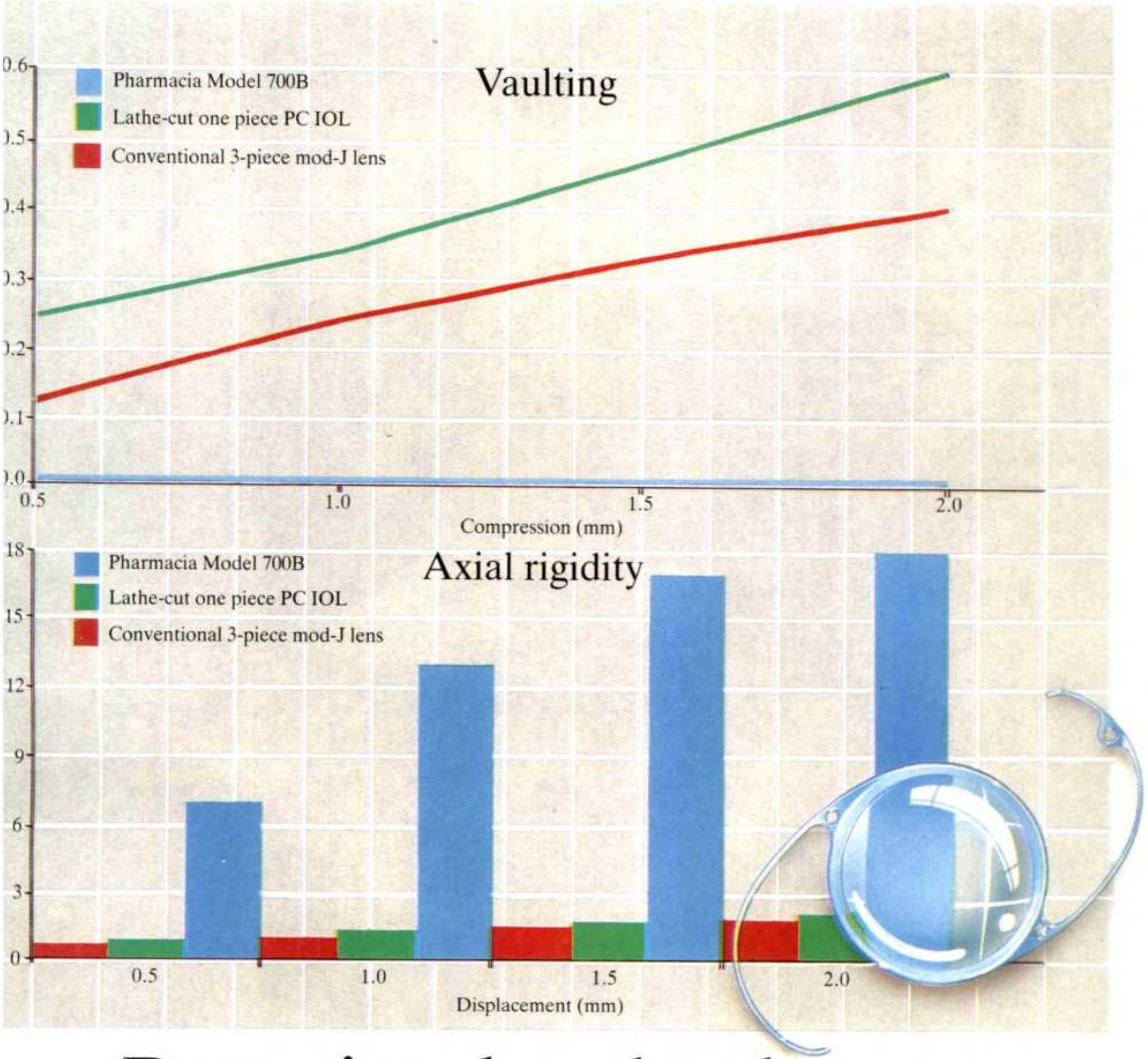
In summary, these patients illustrate the need for complete examination in the face of non-specific or negative findings, so that a correct diagnosis can be made. The ophthalmologist must be aware that potentially malignant lesions may present solely with common ocular symptoms and may be the harbingers of systemic disease.

This study was supported by unrestricted grants from the Frank and Elizabeth Whited Teaching and Research Fund and by Research to Prevent Blindness, Inc.

References

1 McGavic JS. Lymphomatoid diseases involving the eye and its adnexa. *Arch Ophthalmol* 1943; **30**: 179–89.
2 Rosenberg SA, Diamond HD, Jaslowitz B, Craver LF. Lymphosarcoma: a review of 1269 cases. *Medicine* 1961; **40**: 31–76.
3 Yanoff M, and Scheie HG. Malignant lymphoma of the orbit: difficulties in diagnosis. *Surv Ophthalmol* 1967; **12**: 134–40.
4 Knowles DM, Jakobiec FA. Orbital lymphoid neoplasms: a clinicopathologic study of 60 patients. *Cancer* 1980; **46**: 576–89.
5 Cooper EL, Riker JL. Malignant lymphoma of the uveal tract. *Am J Ophthalmol* 1951; **34**: 1153–8.
6 Simon JW, Friedman AH. Ocular reticulum cell sarcoma. *Br J Ophthalmol* 1980; **64**: 793–9.
7 Vogel MH, Font RL, Zimmerman LF, Levine RA. Reticulum cell sarcoma of the retina and uvea. *Am J Ophthalmol* 1968; **66**: 205–15.
8 Gass JDM, Sever RJ, Grizzard WS, *et al.* Multifocal pigment epithelial detachment by reticulum cell sarcoma. *Retina* 1984; **4**: 135–43.
9 Margolis L, Fraser R, Lichter A, Char DH. The role of radiation therapy in management of ocular reticulum cell sarcoma. *Cancer* 1980; **45**: 688–92.
10 Lewis RA, Clark RB. Infiltrative retinopathy in systemic lymphoma. *Am J Ophthalmol* 1975; **79**: 48–52.
11 Hartshorne I. Lymphosarcoma of the orbit probably arising in the choroid. *Am J Ophthalmol* 1922; **5**: 604–8.
12 Chambers JD, Mosher ML. Intraocular involvement in systemic lymphoma. *Surv Ophthalmol* 1966; **11**: 562–4.

Accepted for publication 10 February 1987.



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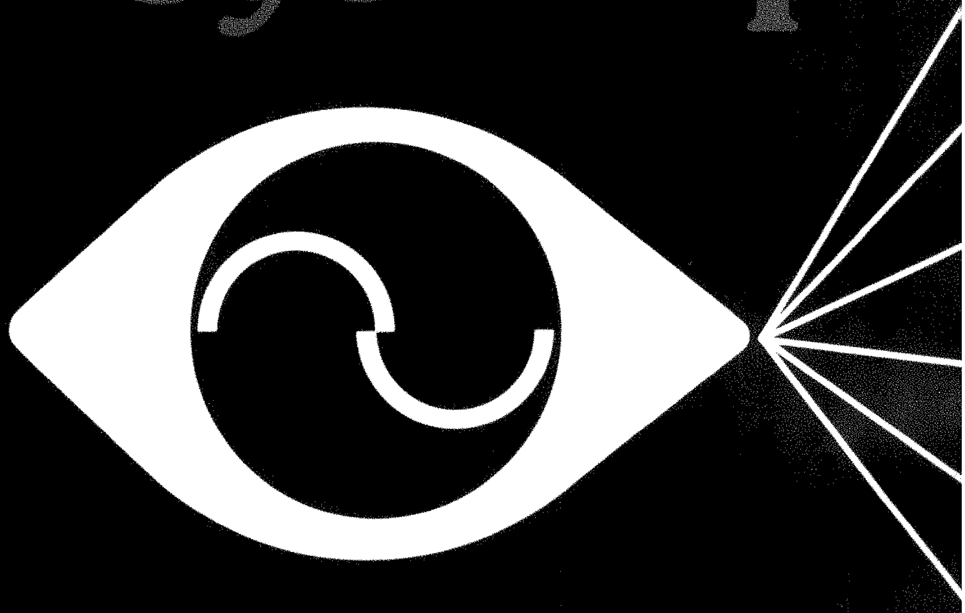

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Postural changes in perfusion pressure and retinal arteriolar calibre

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SUMMARY Ophthalmic artery perfusion pressures and retinal arteriolar calibres were studied in 10 human subjects when sitting, standing, and lying. Differing responses in perfusion pressure were found; autoregulatory responses were found in 13 of the 18 significant calibre changes on moving from sitting to standing and 13 of 22 significant calibre changes on moving from standing to lying. The remaining significant calibre changes were non-autoregulatory, the arterioles dilating with perfusion pressure increase and constricting with decrease.

Autoregulation, the intrinsic tendency to maintain constant blood flow despite changes in perfusion pressure, occurs in many tissues, protecting their metabolic requirements.

Changes in posture are associated with alterations in perfusion pressure. On standing, arterial blood pressure at the head drops by 20–30 mmHg and the jugular venous pressure decreases by 5–8 mmHg. Cerebral vascular resistance also falls because of the decrease in intracranial pressure. The resulting decrease in cerebral blood flow leads to an increase in local P_{CO_2} and a decrease in P_{O_2} and pH. These metabolic changes lead to vasodilatation and an associated restoration of adequate blood flow. The constancy of cerebral blood flow over a wide variety of conditions is a striking feature of its physiology.[1]

It would seem reasonable to speculate that the retina, sharing a common embryological origin and a high metabolic demand, should show a similar capacity to autoregulate. Support for this hypothesis has been given by a small number of studies of the human retinal circulation. Russell[2] reported an increase in retinal arterial calibre in response to an acute increase in intraocular pressure induced by applying pressure to the globe. This occurred both in patients with a normal vascular innervation and in those with Horner's syndrome. Dobree[3] found that, when intraocular pressure was decreased either by drugs or by operation in patients with glaucoma, retinal arterial and venous constriction occurred. Riva and Loebl,[4] using the blue light entoptic phenomenon to measure human macular blood flow, recorded autoregulation in response to a change in perfusion pressure. The average time lag of the response was 46 seconds and the duration of the response was about 48 seconds.

In this study posture was chosen as a physiological stimulus to an alteration of perfusion pressure. The circulatory problems of the eye are unique. The venous pressure elsewhere in the head and neck becomes negative with respect to atmospheric pressure on standing. Gravity would be assumed likewise to decrease venous pressure in the eye, but this must always be maintained above the intraocular pressure.[5]

It is of additional interest to study the retinal vasculature in relation to posture, since many retinal venous occlusions present in the morning after lying down overnight. In addition such patients often notice a diurnal variation in their vision, seeing less well in the morning. Pathologically high increases in intraocular pressure on adopting a supine posture have been associated with retinal vein obstructions[6] and suggested as a high risk factor for the development of chronic simple glaucoma in patients with ocular hypertension.[7]

The purpose of this study was to investigate the changes of calibre in retinal vessels in relation to body posture. Alterations in vessel calibre can be taken as an indicator of autoregulation occurring in the retinal vascular bed if other metabolic influences can be assumed to be constant.

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Materials and methods

Ten normal subjects (eight male and two female) aged 28–34 years were investigated. Subjects were excluded from the study if they suffered from any cardiovascular or respiratory disease or were taking any medication with cardiovascular effects. (One subject did suffer from migraine but had not had a recent attack and did not give rise to results which stood apart from the rest of the group.) All subjects were non-smokers. At the start of each study the subject was seated at the Zeiss (Oberkochen) fundus camera. All measurements were taken with the subject's pupil dilated (both for calculation of perfusion pressures and for vessel measurement).

After a period of cardiovascular stabilisation during which brachial blood pressure (mercury sphygmomanometer) and pulse rate were measured a series of five red-free fundus photographs centred on the optic disc were recorded. Each photograph was timed to mid-diastole by linking the camera shutter to the pulse recorded at the finger. At the end of each series of photographs the intraocular pressure was recorded with the Perkins hand-held tonometer. This method of tonometry was chosen to allow measurement of intraocular pressure in various body postures and in close temporal relationship to fundus photography. The subject was then asked to stand, and after a further period of cardiovascular stabilisation a further set of photographs was recorded and then the intraocular pressure. This procedure was then repeated with the subject lying on his/her right-hand side with the sphygmomanometer cuff on the upper arm. In all subjects the left eye was studied. Individuals with a refractive error greater than 3 dioptres were included in the study as the consequent difference in fundus magnification would not affect the proportional changes in calibre.

On a subsequent occasion the diastolic ophthalmic artery pressure was estimated. It was not possible to obtain this measurement at the same time as the photography was done, since the inevitable corneal distortion and drying associated with the application of the scleral suction cup was found to reduce the quality of the photographs. A modified Langham scleral suction cup was applied to the temporal sclera of the left eye with the subject seated at the fundus camera, thus reproducing the conditions of the photographic session and facilitating visualisation of retinal vessels. The suction pressure was increased until diastolic collapse of the arterial vessels at the disc was noted. Recordings were made three times in each of the three postures. The subject was then seated at the slit-lamp and the suction cup reapplied. The suction pressure was increased to the mean of the three suction pressures recorded at the camera for each posture and the corresponding intraocular pressure recorded with the Goldmann tonometer.

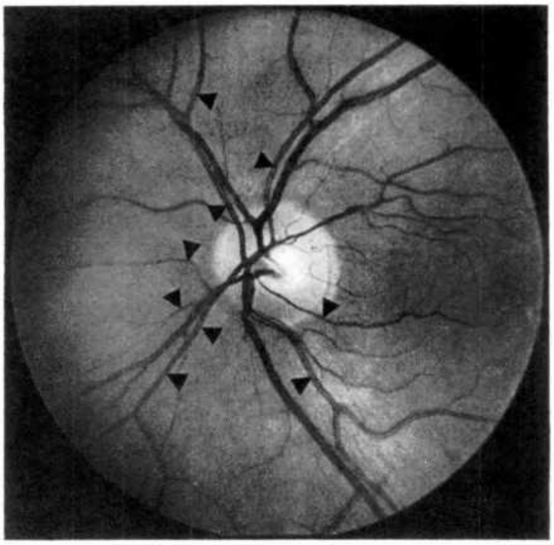

Fig. 1 *A typical retinal photograph showing the sites of calibre measurements.*

Measurements of retinal vessel calibre were made with the Quantimet 800 Image Analyser (Cambridge Instruments) with 1D autoanalyser. Careful densitometric control of the photographs maintained the accuracy of the technique.[8] Calibre measurements were made at sites in the central portion of the photographic field, avoiding the optic disc (Fig. 1).

Results

POSTURE AND PERFUSION PRESSURES

Table 1 shows the ratio of the diastolic brachial blood pressure (DBP) and the intraocular pressure (Dyn P) corresponding to the diastolic dynamometry suction pressure for each posture in each subject. The DBP is the mean of the last four readings taken before photography in each posture. The mean ratios with their standard deviations (SD) are shown at the foot of Table 1. There is a constant ratio in the sitting and standing postures (0·62, 0·65 respectively), but the lying position produces a higher ratio (1·03) with a larger individual variation (SD±0·28).

Table 2 shows the estimated retinal artery perfusion pressures (PP). These perfusion pressures were the product of the mean Dyn P/DBP ratio (using the DBP recorded at the dynamometry session) and the diastolic blood pressure recorded during the photographic session, minus the intraocular pressure (also recorded during the photographic session).

Table 1 *Brachial diastolic and dynamometry pressures (mmHg)*

Subject	*Sit*			*Stand*			*Lie*		
	DBP	*Dyn P*	*Ratio*	*DBP*	*Dyn P*	*Ratio*	*DBP*	*Dyn P*	*Ratio*
1	87	52	0·60	99	52	0·53	66	60	0·91
2	67	42	0·63	78	52	0·67	70	60	0·86
3	79	53	0·67	72	58	0·81	55	68	1·24
4	72	44	0·61	74	49	0·66	67	58	0·87
5	70	50	0·71	74	46	0·62	74	60	0·81
6	74	48	0·65	79	46	0·58	64	55	0·86
7	82	45	0·55	74	48	0·65	41	56	1·37
8	73	42	0·58	71	50	0·70	40	56	1·40
9	66	39	0·59	69	45	0·65	45	60	1·33
10	79	51	0·65	95	56	0·59	91	58	0·64
Mean	74·9	46·6	0·62	78·5	50·2	0·65	61·3	59·1	1·03
SD	6·74	4·86	0·047	10·23	4·34	0·076	16·17	3·67	0·276

ARTERIOLAR CALIBRE CHANGES

A total of 71 arteriolar sites were measured with a range of 4–9 sites for each subject. Five replication photographs were measured for each posture in all but one instance, where only four replications were available. Measurements were recorded in µm at the image of the film. As regards the magnification factor for the Zeiss Fundus Camera,[9] 1 mm on the film is equivalent to 0·45 mm on the fundus in the emmetropic eye; thus the mean calibre measured, 237·4 µm at the film, is equivalent to 106·8 µm at the fundus.

A row and column analysis of variance (ANOV), with replications, was carried out for each subject, the rows representing different postures, the columns different sites. A significant R×C interaction was revealed in all but one subject (10), and in this case the variance within columns showed a highly significant difference ($p<0{\cdot}001$) by Bartlett's test. The results were therefore broken down by sites and tested by one-way ANOV, between and within postures. Thirty one sites scattered among the 10 subjects showed significant variance between postures, tested by the F ratio at the 5% level. The confidence limits (CL) varied from site to site and are shown in a cumulative frequency histogram (Fig. 2). The left ordinate scale shows percentage change, referred to the mean of all calibres measured, the right ordinate scale the change in µm at the film; 50% of the significant changes were detected when the calibre altered by 6% or less, the median figure being 14·3 µm at the film.

The least significant difference (LSD) for each one-way ANOV, was calculated at the 5% level (LSD=standard error, difference of means×t, where t has the degrees of freedom within the three postures), and those changes of calibre which exceeded this value were selected for further consideration. Derived from the 31 significant sites, a total of 18 changes in the 'sit-to-stand' posture shift, and 22 in the 'stand-to-lie' shift, were considered in the final analysis; their mean values and 95% confidence

Table 2 *Estimated perfusion pressures*

Subject	*Perfusion pressure (mmHg)*			*% Change*	
	Sit	*Stand*	*Lie*	*Sit Stand*	*Stand Lie*
1	46	47	46	+2·2	−2·1
2	32	43	58	+34·4	+34·9
3	40	38	42	−5·0	+10·5
4	33	38	52	+15·2	+36·8
5	24	34	60	+41·7	+76·5
6	39	42	51	+7·7	+21·4
7	42	33	28	−21·4	−15·2
8	31	33	25	+6·5	−24·2
9	31	36	31	+16·1	−13·9
10	31	49	77	+58·1	+57·1
Mean change				+15·6	+18·2
95% confidence limits				±16·8	±23·8

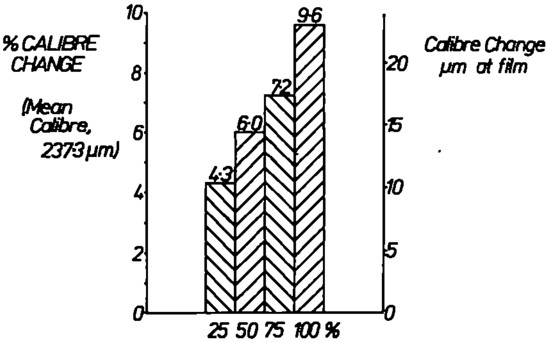

Fig. 2 *5% confidence limits for significant arteriolar calibre changes.*

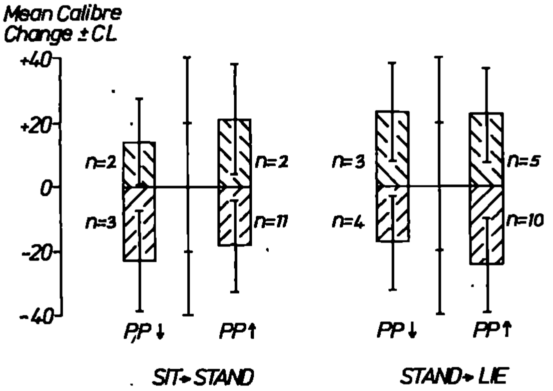

Fig. 3 *Perfusion pressure and arteriolar calibre changes for the two posture changes studied.*

limits are shown in Fig. 3. The results have been separated according to the accompanying perfusion pressure shift and the resultant calibre increase or decrease. The number of significant changes represented in each histogram bar is indicated, and the 95% confidence limits are shown by the line spanning the histogram block.

Because of the range of calibres of the arterioles measured (159–340 µm at the film), the proportional change is more relevant to possible physiological significance than is absolute calibre change, though the latter is appropriate for assessing statistical significance. Figs. 4 and 5 show the individual significant changes, expressed as percentages, plotted against the percentage perfusion pressure change for the posture alterations sit-to-stand and stand-to-lie respectively. Each plotted ordinate represents the changes in one subject and is shown with a different symbol. Only nine subjects are recorded in Fig. 4 as one (6) showed no significant changes on this posture shift.

An autoregulatory response would be represented by calibre decrease when the perfusion pressure rises and calibre increase when the perfusion pressure falls. Inspection of Fig. 4 shows 11 autoregulatory changes when the perfusion pressure rises and two when it falls; there are also five apparently non-autoregulatory changes where the calibre follows the increase or decrease in perfusion pressure. Similarly in Fig. 5 there are 10 autoregulatory changes with perfusion pressure increase and three associated with perfusion pressure decrease. There are also nine non-autoregulatory changes. The proportion of autoregulatory changes to non-autoregulatory changes when the perfusion pressure rises is smaller in the stand-to-lie shift (10:5) than in the sit-to-stand shift (11:2). In Fig. 5 three subjects show significant calibre changes in both directions, increase and decrease.

Discussion

Perfusion pressures have been recorded in terms of the diastolic blood pressure, as only the diastolic dynamometry pressure was recorded, to reduce the degree of disturbance to the background intraocular pressure produced by the scleral suction cup. The calibres also were measured in diastole to avoid complications of pulsatile variation.

The larger DBP/Dyn P ratio when lying (Table 1) can be explained in hydrostatic terms; for the vertical distance from heart to eyes is approximately 300 mm when sitting and standing, but abolished when lying, while the brachial sphygmomanometer cuff is about level with the heart when sitting and standing, but 100 mm above when lying to face the camera with the cuff on the upper arm. If these distances are scaled to equivalent pressure changes in mmHg, the mean DBP lying must be increased (61·3+7 mmHg, and the mean Dyn P decreased (59·1−22 mmHg) to reach

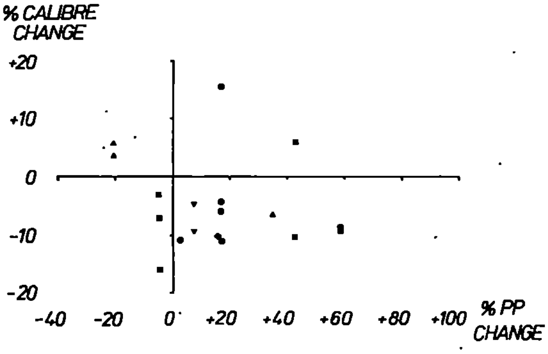

Fig. 4 *Percentage perfusion pressure and arteriolar calibre change for the sit-to-stand posture change. Each column of symbols represents calibre changes for one subject.*

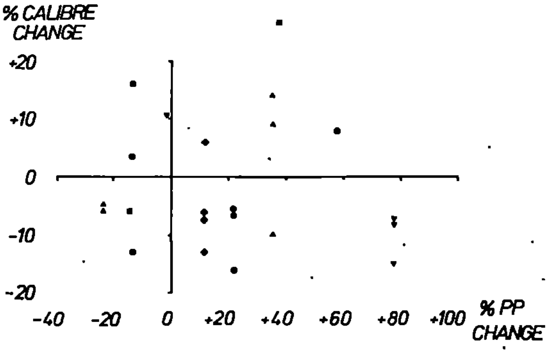

Fig. 5 *Percentage perfusion pressure and arteriolar calibre change for the stand-to-lie posture change. Each column of symbols represents calibre changes for one subject.*

values equivalent to those in the sitting and standing positions. The resultant ratio after this adjustment, 0·54, is comparable to the original sitting and standing ratios.

Whatever technique is used to measure the apparent calibre of retinal vessels, the errors in measurement relate principally to the uncertainty of the vessel edge. They tend to be constant in absolute magnitude while increasing proportionally as the measured calibre decreases. For this reason statistical analysis was performed on the actual measurements of the film, though proportional, percentage changes were used at a later stage to aid comparison of significant vessels of different sizes.

A total of 142 calibre changes were recorded (two for each site). The mean value for an increase in calibre was 10·4 µm, SD 8·96, and for decrease in calibre 12·7 µm, SD 9·61. Of the significant changes the median value for the LSD was ±14·3 µm. This relatively large figure attributable to the collective errors of measurement from photography and image analysis accounts for the reduction from 71 sites measured to 31 sites showing significant changes at the 5% level.

While the majority of calibre changes (13 out of 18, in the sit-to-stand shift, and 13 out of 22 in the stand-to-lie shift) accord with an autoregulatory response, calibre decreasing when the perfusion pressure rises, and increasing when it falls, there are a considerable number of non-autoregulatory responses, particularly following perfusion pressure rise in the stand-to-lie shift which appear to be passive in nature, the calibre increasing with an increase of perfusion pressure. The presence of a considerable background variance makes it inevitable that a significant change of calibre can be detected only at those sites where a relatively large alteration has occurred. Nevertheless the confidence limits for the significant calibre changes (Fig. 3) fall well clear of the zero line in all but one instance, supporting the concept that distinct increases and decreases of calibre have occurred. Additional evidence for this conclusion is afforded by the row and column interaction in the two-way analysis of variance which reached the 0·1% significance level in five subjects. This suggests that, even where individual calibre changes did not reach a significant level, there was a trend for changes in both directions to occur.

The topographical location of sites showing non-autoregulatory responses was examined and no repeatable pattern or particular regional distribution was found. Evidence for the mode of response of individual sites on successive changes in posture is fragmentary, but in subjects showing similar changes in perfusion pressure at each posture alteration three sites showed significant changes on both occasions, and in each instance the changes were dissimilar, the arteriole dilating on one occasion and constricting on the other. These observations suggest a random incidence of non-autoregulatory response, both in time and in topographical location.

Our investigation was originally planned to study the established state of the retinal circulation under altered conditions of perfusion pressure induced by changes in body posture: 26 out of 40 significant arteriolar calibre changes showed an autoregulatory response. The results of this study have not fully elucidated the nature of the arteriolar response, which will require further study.

Miss S Hague was supported by the Smith and Nephew Foundation. This study was supported by the Royal National Institute for the Blind. We are also grateful to colleagues at Moorfields Eye Hospital who participated in the study and to the technical staff of the Ophthalmology Department at the Royal College of Surgeons.

References

1 Harper AM. Physiology of cerebral blood flow. *Br J Anaesth* 1965; 37: 225–35.

2 Russell RWR. Evidence for autoregulation in the human retinal circulation. *Lancet* 1973; ii: 1048–50.

3 Dobree JH. Calibre changes in retinal vessels occurring in raised ocular tension: circulatory compensation in chronic glaucoma. *Br J Ophthalmol* 1956; 40: 1–13.

4 Riva CE, Loebl M. Autoregulation of blood flow in the capillaries of the human macula. *Invest Ophthalmol Vis Sci* 1977; 16: 568–71.

5 Langham ME. Vascular pathophysiology of the ocular postural response – a pneumatometric study. *Trans Ophthalmol Soc UK* 1975; 95: 281–7.

6 Williams BI, Peart WS. Effect of posture on the intraocular pressure of patients with retinal vein obstruction. *Br J Ophthalmol* 1978; 62: 688–93.

7 Leonard TK, Kerr-Muir MG, Kirkby GR, Hitchings RA. Ocular hypertension and posture. *Br J Ophthalmol* 1983; 67: 362–6.

8 Hill DW, Crabtree A. Vascular calibres. *Trans Ophthalmol Soc UK* 1984; 104: 107.

9 Norton HJ, Sullivan CT. On improving retinal photographic standards. *Arch Ophthalmol* 1958; 59: 746–51.

Accepted for publication 29 January 1987.

British Journal of Ophthalmology, 1988, 72, 258–262

Comparative evaluation of oculokinetic perimetry and conventional perimetry in glaucoma

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SUMMARY Oculokinetic perimetry is a new method of visual field assessment in which the patient moves the eye around a central static target to look sequentially at an array of numbers. When fixation on a number is accompanied by disappearance of the central target, that number is deleted from a recording chart. Inversion of the recording chart gives a plot of the central visual field. In this study we have shown that in 64 eyes of 37 patients, with unequivocal field loss attending a glaucoma clinic, the test is efficient and reliable when compared with conventional static (Dicon 3000) and kinetic (Tübingen Oculus) field tests. The results were identical in 88% of eyes tested and approximately comparable in another 6%. Quantitative equivalent targets for the different methods are described. Oculokinetic perimetry was carried out by a previously untrained person, and it is suggested that this new method merits further study as a screening device for glaucoma in the community.

A recent review[1] of currently available methods of visual field analysis suggests that there is as yet no ideal method for glaucoma screening. In particular, there is still a need for a skilled observer to administer the tests. The ideal perimeter should be reliable, provide precise detection and assessment of field loss, and be available at reasonable cost. Oculokinetic perimetry (OKP) is a novel method which promises to meet all these requirements.[2,3] It consists of a white tangent screen with a series of numbered fixation targets located at various points in relation to the test stimulus. The distribution of these numbers is such that the central test stimulus is displaced into different points in the central 25° of field as the eye follows the numbered sequence. The numbers are arranged in 16 meridians at 2·5 to 5·0 degree intervals. There is no need for manual or mechanical presentation of the test stimulus, and electronic or visual monitoring of the subject's eye movements is unnecessary. Disappearance of the test stimulus is recorded on a miniature version of the test chart to produce a result which is inverted for interpretation.

A previous study[2] has suggested that this test is simple enough for it to be performed by unsupervised persons. We now report its effectiveness in patients with known glaucomatous field loss and compare the results with those obtained by conventional and kinetic perimetry.

Patients and methods

The 37 patients in this study (28 males and 9 females) were between 40 and 85 years of age, average 65 years. Twenty-five patients had primary open angle glaucoma, six chronic angle closure, two low tension, two juvenile, one traumatic, and one steroid induced glaucoma. In 10 patients only one eye was examined because of reduction of vision in the fellow eye to less than 6/12 as a result of cataract (six eyes), senile macular degeneration (three eyes), and amblyopia (one eye).

OKP was compared with kinetic central 30° analysis in the Tübingen Oculus perimeter in 25 patients, and with static testing on the Dicon 3000 perimeter using a two-zone strategy glaucoma pattern in the central 30° of the visual field. All patients had unequivocal glaucomatous visual field loss demonstrated by one or both of the conventional tests. Table 1 shows the stimuli used together with background illumination and approximate Goldmann equivalents. Oculokinetic perimetry was performed in a glaucoma clinic in the position normally occupied by the Bjerrum screen. This was illuminated by two 20 watt fluorescent tubes in an

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Table 1 *Correlation of test stimuli for OKP, Dicon 3000, and Tübingen Oculus. The appropriate Goldmann equivalent is also stated*

	Stimulus designation			*Approximate Goldmann equivalent*
	OKP	*Tübingen Oculus*	*Dicon 3000*	
Minimum test stimulus	2 mm	1·0 W/05	100 asb	I-2e
Maximum test stimulus	6 mm	1·0 W/00	1000 asb	I-4e
Background illumination	122 asb	10 asb	10 asb	31 asb

Table 2 *Classification of visual field defects according to minimum stimuli of: 2 mm target for OKP, 1·0 W/05 for Tübingen Oculus, and 100 asb for Dicon 3000*

Severity of field loss	*Definition*
Mild	Arcuate scotoma but central 10° visual field normal
Moderate	Visual field defect within 10° of fixation
Severe	Visual field defect within 5° of fixation

angled reflector 2·5 m from the screen, in addition to illumination by two 80 watt fluorescent tubes at 3·4 m from the screen. A Weston light meter held at 1 m from the screen indicated a reflected light of 122 asb. Preliminary investigation had tested the response of two patients with mild and severe field loss respectively at a lower level of illumination (33 asb) corresponding to a 100 watt tungsten filament bulb 2·2 m from the screen. This level of illumination was selected in order to reproduce average domestic lighting conditions.

On the day of the investigation patients were tested with either the Dicon 3000 or the Tübingen Oculus by a skilled perimetrist, and also by OKP by an ophthalmologist with no previous experience with this test. The test to be performed first was chosen at random, and an interval of at least 10 minutes was allowed between the two tests. OKP was performed after a brief verbal introduction with the patient seated at a desk with one eye occluded and at a working distance of 1 metre. The right eye was always tested first, so that any fatigue effect in the second eye might be more easily identified. The subject was asked to look at each number in a sequence from 1 to 100 taking about one second per number, and to identify the numbers which were associated with the disappearance of the test stimulus. The central target was a circular black spot of either 2 mm or 6 mm diameter. This was attached to the test screen by means of a magnet and changed as required. The 2 mm stimulus was always presented first. The results were noted in a special record chart by the perimetrist beginning with the physiological blind spot. The time required to test each eye was recorded, although in the case of the Dicon 3000 the print-out time of 2 minutes was not included. The perimetrist also noted the degree of patient co-operation and concentration.

The severity of visual field loss was categorised as shown in Table 2, with minimum stimuli of 2 mm (OKP), 1·0 W/05 (Tübingen Oculus stimulus designation) and 100 asb (Dicon 3000 stimulus designation). For standardisation, conventional fields were performed with these minimum stimuli and also with maximum stimuli of 6 mm (OKP), 1·0 W/00 (Tübingen Oculus stimulus designation), and 1000 asb (Dicon 3000 stimulus designation). The correlation for minimum and for maximum stimuli between the three methods was established before starting the study. The results of OKP were compared to those of conventional perimetry by one of the authors, who had not himself tested the patients. The comparison was considered satisfactory if (*a*) the visual fields were identical in both tests (grade I) or (*b*) there were field defects in the same area that differed in extent and density (grade II). Unsatisfactory correlation was designated grade III.

Three pairs of oculokinetic and Tübingen Oculus and three pairs of oculokinetic and Dicon 3000 visual fields showing various degrees of correlation were made up artificially and included as controls to assess the reliability of the independent observer (JLS).

Results

Preliminary studies of the two patients with mild and severe visual field loss respectively at 122 asb and 33 asb showed no difference in the extent of field defect detected. All further tests were carried out at the higher level of illumination.

All patients who began OKP and conventional perimetry were able to complete the examinations. In OKP the average time taken per eye to complete the test with two isoptres was 7 minutes. In both Tübingen Oculus and Dicon 3000 perimeters the average time per eye was 8 minutes. The blind spot was plotted first, and in OKP, as in other tests, this was found to be a good indicator of the reliability of the test. The degree of correlation of the different methods of perimetry in relation to the severity of visual field loss is shown in Table 3. Results were available for 64 eyes of 37 patients. In 56 eyes the correlation between the fields was grade I. Figs. 1 and 2 show the charts of two such patients. Four eyes were assigned to grade II, and another four eyes grade III. All six pairs of control field charts were matched correctly by the independent observer. The severity of field loss did not seem to effect the reliability of the test (Table 3).

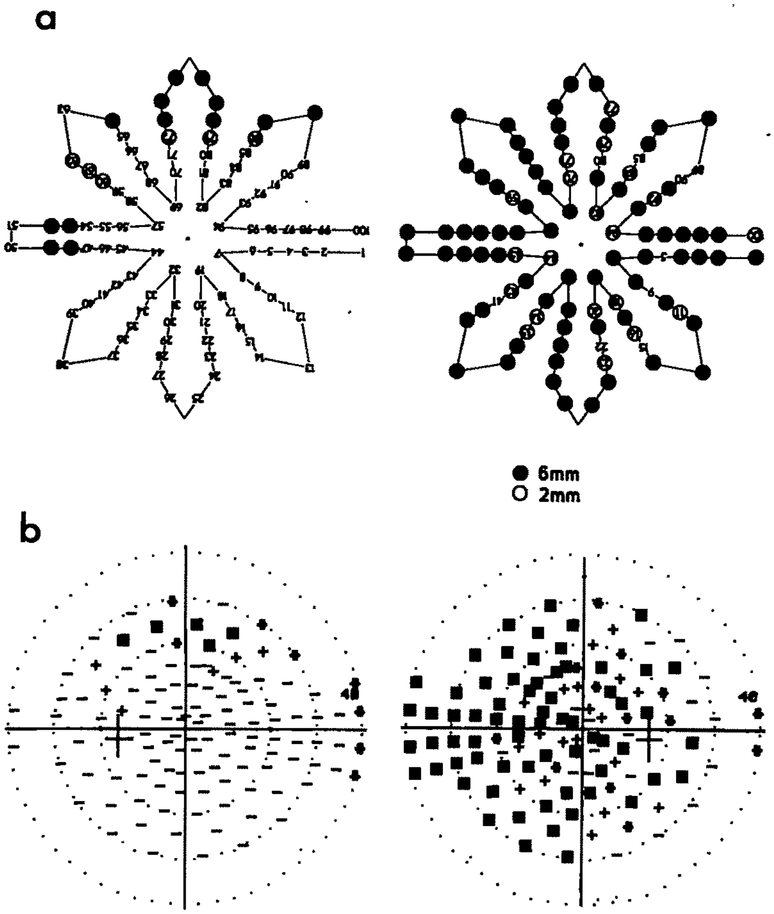

Fig. 1 *The visual fields of a 65-year-old male patient with severe visual field loss in the right eye and mild visual field loss in the left eye, as plotted* (a) *by OKP and* (b) *by Dicon 3000 perimeter. The patient was assigned grade I correlation. The scale of* (b) *appears smaller because of the wider 40° field display.* ■*=1000 asb. +=100 asb. −=seen point.*

Table 3 *Degree of correlation between OKP and conventional perimetry in 64 eyes of 37 patients*

Degree of correlation	*Extent of field loss*			*Total number of eyes*
	Mild	*Moderate*	*Severe*	
Fields identical (grade I)	30	13	13	56
Defects in same area but different in extent and density (grade II)	3	0	1	4
No recognisable similarity (grade III)	2	1	1	4
Total	35	14	15	64

There were two patients with poor concentration showing grade I correlation in both eyes. There were two other patients with poor concentration, but they produced only grade III correlation in one eye, while showing grade I correlation in the fellow eye (Table 4). Both of the last two patients had reliable results on the Tübingen Oculus perimeter when tested previously in the glaucoma clinic. On this occasion one of these patients had Tübingen field results comparable to those obtained in the past, while for the other patient neither his Tübingen nor OKP fields resembled his previous visual fields. In a third patient with poor correlation, retrospective analysis of his Dicon fields in the glaucoma clinic showed variable results. Table 4 summarises the findings of all three patients with grade III correlation.

Discussion

Our results show that OKP, if performed correctly, can produce results comparable with those obtained with conventional perimetry regardless of the severity of the field defect. Using 2 mm and 6 mm spot targets we found the method surprisingly quantitative and able to discriminate between different densities of field loss in a fashion comparable to

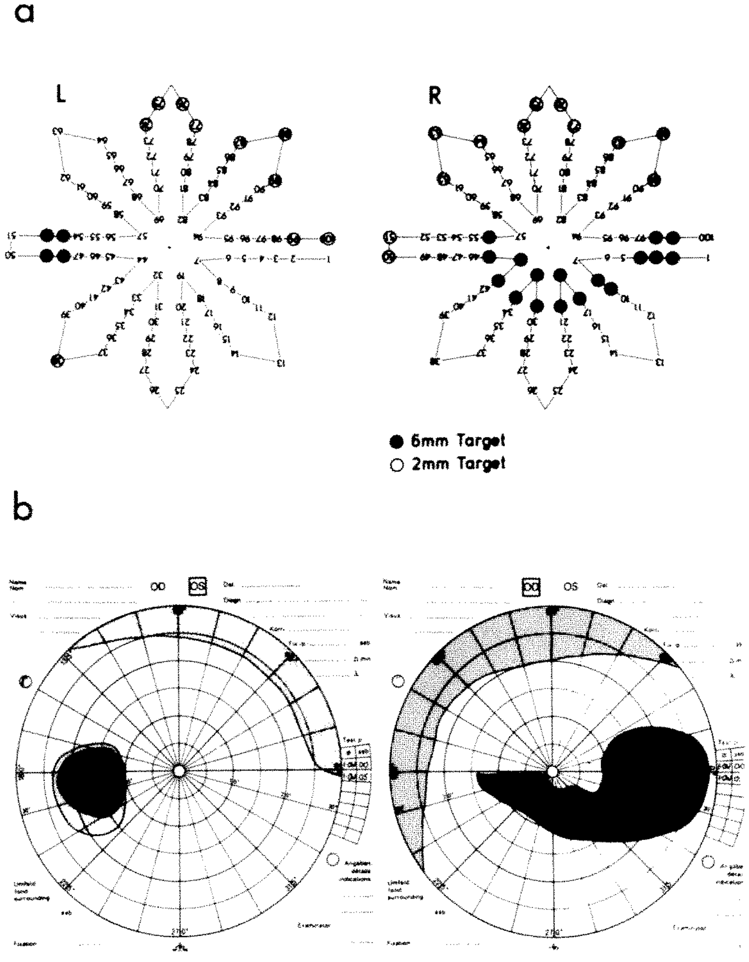

Fig. 2 *The visual fields of a 60-year-old female patient with mild field loss in the left eye and severe field loss in the right eye as plotted* (a) *by OKP and* (b) *by Tübingen Oculus perimeter. The patient was assigned grade I correlation.*

selected isoptres on the other perimeters. Excellent correlation (grade I) was found in 88% of eyes tested and a useful degree of correlation was noted in an additional 6%, indicating that the method is much more accurate than its simple design might suggest.

The method is not time consuming. On average OKP required two minutes less than the other perimeters to examine both eyes, and it must be remembered that this OKP time is for a first and unfamiliar test in comparison with a familiar form of

Table 4 *Details of patients with poor correlation of visual field tests using different methods. The left eye of patient 1 and the right eye of patient 2 showed good correlation (grade I)*

Patient	*Sex*	*Age (years)*	*Grade III correlation (circled)*	*Diagnosis*	*Corrected visual acuity*	*Conventional perimeter*	*Degree of field loss*	*Degree of concentration*
1	M	55	Ⓡ L	POAG POAG	6/6 6/6	Tübingen Oculus	Severe Severe	Poor Poor
2	M	79	R Ⓛ	POAG POAG	6/6 6/6	Tübingen Oculus	Severe Severe	Poor Poor
3	M	59	Ⓡ Ⓛ	POAG POAG	6/9 6/6	Dicon 3000	Severe Mild	Good Good

POAG = primary open angle glaucoma.

conventional test. With familiarity OKP should prove faster and might even be performed without supervision. It would also be possible to administer this test to more than one patient simultaneously if a 'classroom' area was available to provide the required space for desks and charts. OKP therefore seems to have significant advantages if reducing the time required to test visual fields is a priority. The ambient illumination may vary depending on whether OKP is performed in outpatient clinics, community clinics, or in the patient's home. However, our pilot study suggests that variation in ambient illumination does not affect the result.

Poor co-operation limited the accuracy of the test in only two patients (3%), a figure very similar to what we expect in conventional tests on the elderly glaucoma population. As in other forms of perimetry, plotting the physiological blind spot in OKP is a good guide to reliability. Although it is initially necessary to observe the patient's fixation to ensure the test is properly understood, Damato[2] has shown that once the patient is familiar with the test it is not necessary to continue doing so.

We thank the Department of Medical Illustration at the Western Infirmary, Dr D Allan, and Mrs S M Mitchell for their assistance.

This study was supported by the Visual Research Trust, Glasgow.

References

1 Editorial. Current status of automatic perimetry. Is the ideal automated perimeter available? *Arch Ophthalmol* 1986; **104:** 347–9.

2 Damato BE. Oculokinetic perimetry: a simple visual field test for use in the community. *Br J Ophthalmol* 1985; **69:** 927–31.

3 Damato BE. Assessment of the visual field by anyone, anywhere and at any time. *Trans Ophthalmol Soc UK* 1985; **104:** 681–5.

Accepted for publication 10 February 1987.

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References
1. Zimmerman, T. J., presented at: Int. Symposium on Glaucoma, XIII Int. Co Ophthalmology, Kyoto, Japan, May 1978, 55-64.
2. Sponsel, W. E., *et al., Brit. J. Ophthal.*, 1983, 67, 220-227.
3. Sponsel, W. E., International Symposium on Glaucoma, Turin, 1986.
4. Katz, I. M., presented at: Int. Symposium on Glaucoma, XIII Int. Con Ophthalmology, Kyoto, Japan, May 1978, 29.

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British Journal of Ophthalmology, 1988, **72**, 263–269

Therapeutic limitations of argon laser trabeculoplasty*

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SUMMARY Sixty-one patients (82 eyes) were studied after argon laser trabeculoplasty (ALT) to determine the lasting efficacy of such treatment. This investigation, now in its fourth year, was prospective, and the information derived was analysed with the aid of a computer. Success was defined as intraocular pressure (IOP) below baseline (22 mmHg). The mean follow-up time was 24·5 months, when the success rate was 74% compared with 75% at three months. Success declined to 45% at 42 months. No significant difference was noted when (*a*) first lasered eyes of all patients and those fellow eyes treated were analysed separately, (*b*) when right and left eyes were analysed separately, nor (*c*) when patients were divided into two treatment groups, (I) 100 burns at 1 W, and (II) 65 burns at 850 mW. Eight of 11 eyes showed progressive postlaser field loss despite below-baseline intraocular pressures. ALT is an alternative to carbonic anhydrase inhibitor therapy, with a success rate of 66·7% at two years. However, repeat ALT was successful in only 25% of patients seven months after treatment.

Although argon laser trabeculoplasty (ALT) has proved to be effective for the treatment of many patients with open angle glaucoma, a difference of opinion exists on its lasting benefits. Some reports[1 2] claim continued success, while others[3-5]† have indicated a loss of effect. We published an article in 1984[6] that indicated success with laser trabeculoplasty, though an intraocular pressure (IOP) rise was noted at the end of the follow-up period. This encouraged us to continue following patients up beyond two years and add new patients. The object of this ongoing investigation was to determine: (*a*) whether a longer follow-up might demonstrate further loss of effect, (*b*) whether analysis of the data would allow us to predict the likelihood of success based on type of patient or treatment method, and (*c*) whether ALT continues to be an effective alternative to carbonic anhydrase inhibitor (CAI) therapy.[7]

Material and methods

All patients entered into the study had primary open angle glaucoma. Patients who did not have chronic open angle glaucoma—that is, secondary glaucoma, combined mechanism glaucoma, pseudoexfoliation, etc.—were excluded. Patients were sequentially entered into this study from a private practice setting. We began following up our first patients 42 months ago, with most patients entered at 26–30 months. All the patients were treated by one ophthalmologist (AIF). Preoperative intraocular pressure was defined as the average IOP immediately prior to laser treatment, and after the withdrawal of CAI with patients in that subgroup. The postlaser IOP was measured and slit-lamp examination performed the day after treatment and repeated weekly for one month, biweekly for a second month, and then monthly.

Continuous wave argon lasers (Coherent Radiation Model 800 and Synemed Ophthalas) were used. The method of treatment adopted for patients was similar to that described by Wise and Witter.[8] Patients were divided into two groups. Treatment group I (25 patients) received 100 50 μm burns, with a power that varied between 1·0 and 1·3 W, that were applied for 0·10 second and directed at the mid-

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*This paper was presented at the 121st Annual Meeting of the American Ophthalmological Society, Hot Springs, Virginia 19–22 May 1985.

†Harrison R, Luntz MH: personal communication.

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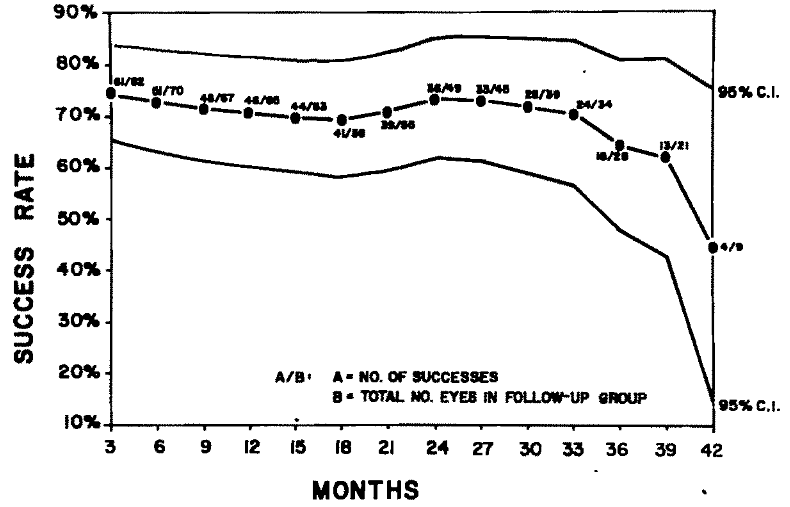

Fig. 1a *Success rate.*

trabecular meshwork. Treatment group II (36 patients) received 65 burns of 800–900 mW at the anterior-to-mid trabeculum.[9 10] All patients continued their prelaser regular medications with the exception of those patients on CAI drugs. We tried to determine whether ALT might be used as an alternative to CAI therapy on 18 patients (27 eyes) who were somewhat intolerant to CAI drugs.[7] All patients were given gentamicin and fluorometholone (FML) drops to be used four times a day in the treated eye. These two medications were discontinued after the first week. The cases were considered successfully treated if they met all of the following criteria: (1) IOP lower than baseline (22 mmHg), (2) no increase in disc cupping, (3) no increase in field loss. The data were analysed with a microcomputer. The mean, standard deviation, standard error of the mean, and analysis of significant (two-tailed *t* test for independent samples) were computed on a microcomputer statistical program. The data were expressed as the mean IOP plus or minus the standard error of the mean (95% CI). The data, including failures, were anlysed up to the point of failure and then with the failures excluded. We also analysed our data excluding failures completely. The data were then compared in three ways: (1) the response of first lasered eyes of all patients (series I) with those fellow eyes treated (series II), (2) the response of right and left eyes

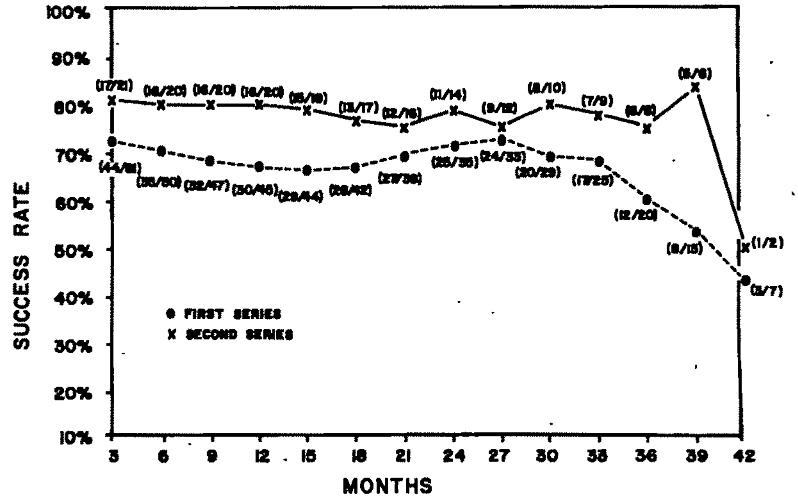

Fig. 1b *Success rate. Data for the first and second series.*

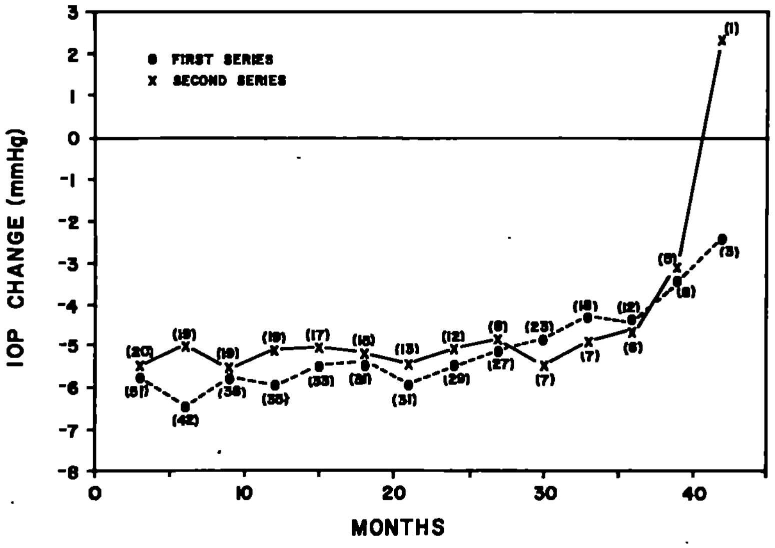

Fig. 2a *Mean drop in IOP with time. Data for first and second series analysed separately (failures included).*

analysed separately, and (3) the response of patients who had been divided into two treatment groups, group I (heavy) versus group II (light). Baseline IOP was defined as 22 mmHg on preoperative medical therapy. Postlaser IOP was the mean IOP on preoperative medications except in those patients in whom we eliminated CAI drugs. Visual fields were checked with a Goldmann perimeter and optic discs photographed every six months.

Results

Eighty-two eyes (41 right and 41 left, from 61 patients) were treated. Fifty-four patients (71 eyes) were white and seven patients (11 eyes) were black. Their mean age was 70·0 years, standard deviation 11·4 years. The mean preoperative IOP was 27·1 mmHg (SD 3·4) for all eyes, while preoperative IOPs for the first and second series were 27·4 mmHg (SD 3·7) and 26·1 mmHg (SD 2·1) respectively. The mean follow-up time was 24·7 months (22·6 for the first series of eyes, 25·7 for the second series), at which time the success rate was 74% for both eyes (71·4% for the first series, 78·6% for the second series). When we plotted success rate over time (Figs. 1a, b), success dropped from 75% for both eyes (71·4% first series, 78·6% second series) at three months to 45% for both eyes (42·9% first series, 50% second series)

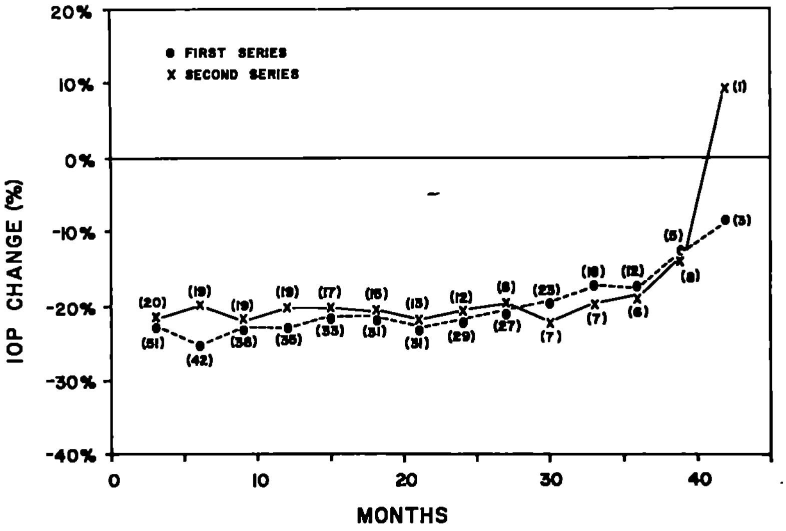

Fig. 2b *Percentage drop in IOP with time. Data for first and second series analysed separately (failures included).*

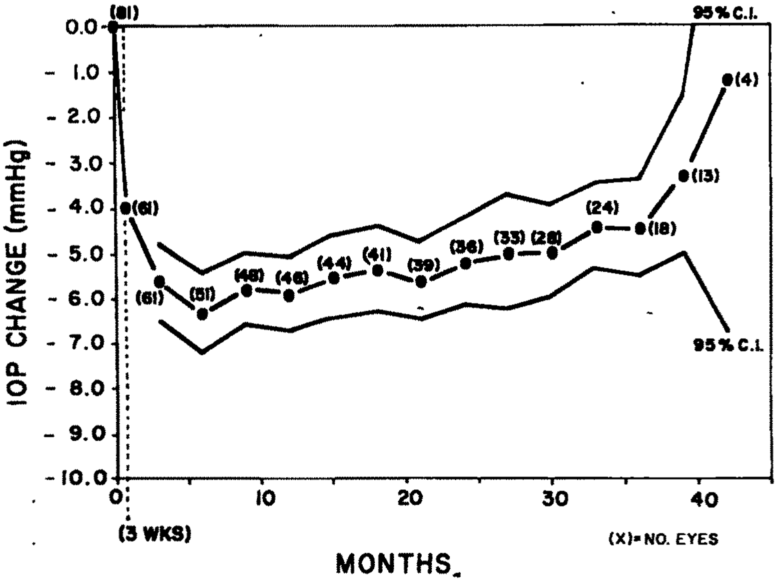

Fig. 3 *Mean drop in IOP with time (failures excluded).*

at 42 months (four successes/nine eyes, two lost to follow-up). The maximum IOP reduction for both series was obtained between six and nine months (Figs. 2a, b). The maximum reduction of each series (−6·4 mmHg first series, −5·5 mmHg second series) attained at this time slowly but steadily decayed until 36 months, when a sharp rise in IOP occurred (Figs. 2a, b). When the data were analysed with the failures omitted, nearly identical curves were obtained (Fig. 3). Eighteen patients (27 eyes) were on CAI drugs before laser therapy. At 24 months 12 of these patients (18 eyes) were able to continue without CAI medication, indicating a success rate of 66·7%±17·8% (95% CI) (Table 1). The patients were divided into two treatment groups. Group II (light treatment) did not show a significantly different response to ALT from group I initially (Fig. 4). However, at 36 months group I maintained significantly lower IOP. Nevertheless, by 39 months the group II patients' IOP reduction decayed to match that of group I.

We measured the IOP 24 hours after ALT, and 6·6% of patients had an IOP rise of 2–10 mmHg (mean 5·5 mmHg) which became normal within three

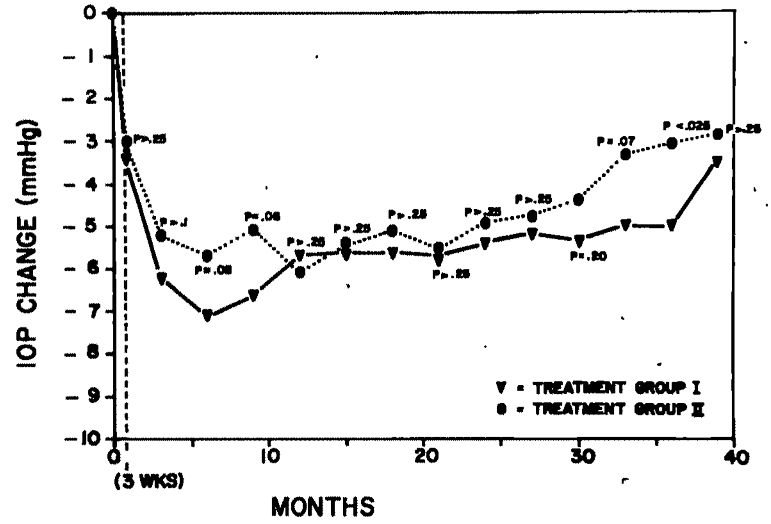

Fig. 4 *Comparison of two treatment groups.*

Table 1 *Response of patients to withdrawal of carbonic anhydrase inhibitor drugs and repeat ALT*

	Number of patients	*Number of eyes*	*Average IOP change (mm)*	*Success rate*	*Average follow-up (months)*
CAI	18	27	−7·2	66·7%	25·6
*Repeat ALT	12	13	−1·1	25·0%	7·0

*Average IOP rise between lasers: 6 mmHg.

Table 2 *Intraocular pressure change by category*

	Treatment group		*Age*		*Blacks*	*Diabetics*
	I	*II*	*≤65*	*>65*		
Max. IOP change (mmHg)	−6·4	−5·1	−5·0	−5·9	−8·8	−7·1
*IOP change (mmHg)	−5·4	−4·9	−4·43	−5·47	−4·8	−4·1
*n=	19	17	10	26	9	6
†p=	>0·25		>0·25		>0·25	>0·25

*Taken at average follow-up time of 24 months.
†Level of significance; T-test for independent samples.

weeks. Group II did not have a significantly lower IOP rise.

When we compared the ALT response of black patients with that of white patients with glaucoma, we found a greater decrease in IOP in black patients but a similar decay curve (Fig. 5). However, the difference was not significant, possibly owing to the small number of black patients in our study. The response of diabetics was compared with that of all patients following ALT (Fig. 6). Initially, diabetics responded as well, but in time averaged an IOP 1 mmHg higher than the entire group (p>0·25). Repeat ALT resulted in a 25% success rate (Table 1).

At 24·7 months 11 of 82 (13·6%) eyes showed progressive field loss. Eight of these 11 eyes had an IOP below baseline and 1/11 was black. The mean prelaser IOP in these eight eyes was 24 mmHg and mean IOP at 27 months was 19·1 mmHg.

There were minimal short-term complications, similar to those already reported by other investigators.[5]

Discussion

Argon laser trabeculoplasty is effective in lowering the IOP in glaucoma patients. There are minimal short-term complications. It may be a satisfactory but temporary alternative to CAI therapy. Our initial success rate of 75% and IOP drop of 23% is consistent with other reports.[11-13] The maximum IOP drop was observed six to nine months after treatment (Figs. 2a, b). The IOP reduction began to diminish steadily, beginning 24 months after treatment. Our 33 months success rate of 71% declined precipitously to 45% at 42 months. While it is true that at 42 months only nine eyes were being followed up (four successes), the change in slope of our success rate began at 33 months, when we were following up 48 eyes. Schwartz and coworkers[5] also demonstrated a similar decay up to four years after treatment.

Most clinical studies[14 15] agree with Wise and

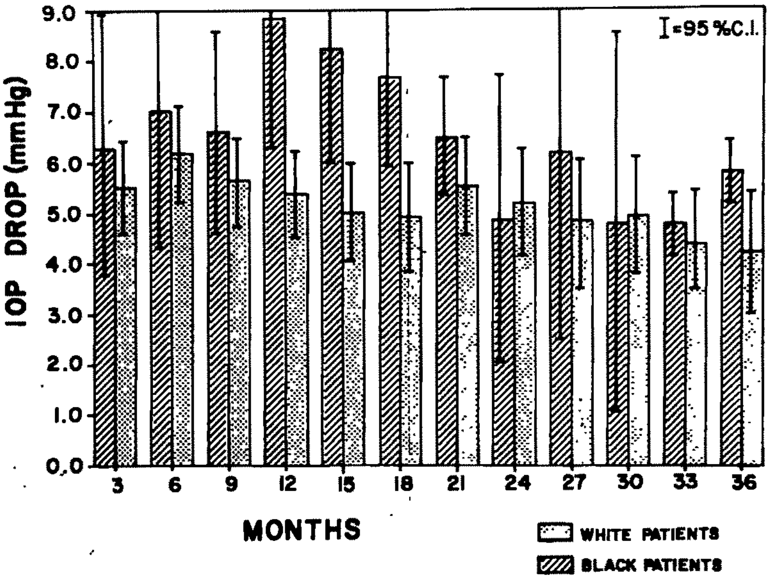

Fig. 5 *Mean pressure drop with time (black versus white patients).*

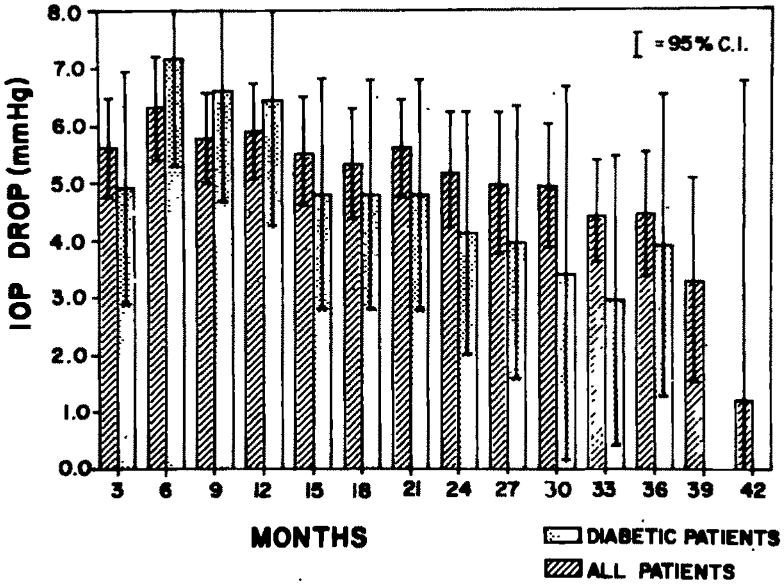

Fig. 6 *Mean pressure drop with time (diabetic versus all patients).*

Witter's[4] hypothesis that laser trabeculoplasty reduces IOP by increasing the coefficient of aqueous outflow. Histopathological and scanning electron microscopic studies of the trabecular meshwork suggested[16] that laser energy may induce, through fibrosis, an inner bowing of the trabecular meshwork to open Schlemm's canal. This finding seems to add credence to Wise's hypothesis that a tightening of the collagenous trabecular ring after laser surgery acts to open the intratrabecular spaces and Schlemm's canal, resulting in decreased resistance to aqueous egress. However, Van Buskirk *et al.*[17] could not demonstrate such a tightening of the collagenous ring in a histological analysis of laser-treated cadaver eyes.

While some of these effects may increase aqueous egress, others may be responsible for ultimate failure of the procedure. More specifically, the loss of trabecular cells at the burn site is of concern. Alvarado[18] suggested that a loss of trabecular cells following laser treatment may ultimately lead to trabecular fushion, increasing resistance to outflow and raising the IOP. This observation might explain why our repeat laser trabeculoplasties, accompanied by a further loss of trabecular cells, have had such little effect (Table 1). Starita *et al.*[19] and Brown *et al.*[20] also observed little effect of repeat ALT. The production of glaucoma by Gaasterland and Kupfer,[21] who lasered the entire trabecular meshwork of rhesus monkeys, has served as a warning that too much laser induced scarring of the trabeculum can increase the IOP. In view of Gaasterland and Kupfer's work and our low success rate, we would advise caution when considering repeat argon laser trabeculoplasty.

Argon laser trabeculoplasty may be an alternative to CAI therapy. Our investigation beginning in 1981 gave a success rate of 76% one year after treatment.[7] Our present mean follow-up time of 24 months demonstrated a 66·7%±17·8% (95% CI) of patients as successful (Table 1).

Postlaser IOP rise has been of considerable concern to ophthalmologists engaged in this therapy,[22–24] and rises of IOP have been present up to six hours after treatment.[13] Krupin and coworkers,[25] who recorded an IOP rise in 53% of their patients, stated that most clinically significant increases of IOP were evident within one hour. Pretreatment with acetazolamide did not significantly alter this response. We tried to reduce the incidence of such IOP rise by reducing the number of burns and decreasing laser energy. However, in spite of these precautions the incidence of IOP rise was not reduced significantly.

Diabetic patients did not respond as well as the general population (Fig. 6). If, as Wise[8] suggests, tightening of the collagenous trabecular ring after laser surgery acts to open intratrabecular spaces, then abnormalities of collagen in diabetics[26 27] may offer some explanation as to why diabetics did not respond as well as other patients.

Older patients have been reported to have a greater and more predictable drop in IOP after trabeculoplasty than younger patients.[5 28] The collapse of an aging flaccid trabecular wall jammed against Schlemm's canal in older patients[29–32] might explain this discrepancy. Tightening of the trabecular ring would thus be expected to have a greater effect on an older population. Our population with a mean age of 70 did not show any difference in IOP drop with age (Table 2), though few of our patients were really 'young'. It is of interest to note that in pigmentary glaucoma it is the younger group that has the greater postlaser IOP decrease.[33]

We cannot draw any valid conclusions with respect to the response to laser by race because we had very few black patients, reducing the statistical validity of our comparison. However, our impression, contrary to that of Schwartz and coworkers,[5] was that black patients did better than whites over the long term. It is interesting to note that Schwartz and colleagues' data may be biased by having very few white patients.

We found visual field loss in eight eyes despite an IOP below baseline. Pohjanpelto[34] found that 15 of 76 eyes with IOP reduction following ALT showed progressive field loss. Our 10% failure rate, and Pohjanpelto's 20% failure rate, despite 'normal' IOP reinforces the need for evaluation of ALT in conjunction with visual field testing, and argues against defining 'success' solely on the basis of IOP.

In spite of the confusion and fragmentary knowledge about the mechanism of action of ALT, it is effective in reducing the IOP in most patients with minimal side effects. The risk/benefit ratio continues to support its use as an alternative to CAI therapy and surgery. ALT may induce structural changes with unknown consequences. However, ALT has deferred the sight-threatening risks and cataractogenic effects of filtering surgery.[35]

References

1 Wickham MG, Worthen DM. Argon laser trabeculoplasty; long-term follow-up. *Trans Am Acad Ophthalmol* 1979; **86:** 495–503.
2 Wise JB. Long-term control of adult open angle glaucoma by argon laser treatment. *Ophthalmology* 1981; **88:** 197–202.
3 Wilensky JT, Weinreg RN. Early and late failures of argon laser trabeculoplasty. *Arch Ophthalmol* 1983; **101:** 895–7.
4 Pollack IP, Robin AL, Sax H. The effect of argon laser trabeculoplasty under medical control of primary open angle glaucoma. *Ophthalmology* 1983; **90:** 785–9.
5 Schwartz AL, Love DC, Schwartz MA. Long term follow-up of argon laser trabeculoplasty for uncontrolled glaucoma. *Arch Ophthalmol* 1985; **103:** 1482–6.
6 Fink AI, Jordan AJ. Laser trabeculoplasty and decay effects in glaucoma. *J R Soc Med* 1984; **77:** 91–101.
7 Fink AI, Jordan AJ, Bunke A, Fong DA. Argon laser trabecular surgery as an alternative to carbonic anhydrase therapy. *Trans Ophthalmol Soc UK* 1982; **102:** 125–8.
8 Wise JB, Witter SL. Argon laser therapy for open angle glaucoma (a pilot study). *Arch Ophthalmol* 1979; **97:** 319–22.
9 Schwartz LW, Spaeth GL, Traverso C, Greenidge KC. Variations of techniques on the results of argon laser trabeculoplasty. *Ophthalmology* 1983; **90:** 781–4.
10 Weinreb RN, Ruderman J, Juster R, Wilensky JT. Influence of the number of laser burns administered on the early results of argon laser trabeculoplasty. *Am J Ophthalmol* 1983; **95:** 287–92.
11 Horns DJ, Bellows AR, Hutchinson BT, Allen RC. Argon laser trabeculoplasty for open angle glaucoma—a retrospective study of 380 eyes. *Trans Ophthalmol Soc UK* 1983; **103:** 288–95.
12 Greenidge KC, Spaeth GL, Fiol-Silva Z. Effect of argon laser trabeculoplasty on the glaucomatous diurnal curve. *Ophthalmology* 1983; **90:** 800–4.
13 Hoskins HD, Hetherington J, Minckler DS, Lieberman MF, Shaffer RN. Complications of laser trabeculoplasty. *Ophthalmology* 1983; **88:** 796–9.
14 Schwartz AL, Whitten ME, Bleiman B, Martin D. Argon laser trabecular surgery in uncontrolled phakic open angle glaucoma. *Ophthalmology* 1981; **88:** 203–12.
15 Brubaker RF, Liesgang TJ. Effect of trabecular photocoagulation on the aqueous humor dynamics of the human eye. *Am J Ophthalmol* 1983; **96:** 139–46.
16 Rodriguez MM, Spaeth GL, Donohoo P. Electron microscopy of argon laser therapy in phakic open angle glaucoma. *Ophthalmology* 1982; **89:** 198–209.
17 Van Buskirk EM, Pond V, Rosenquist RC, Acott TS. Argon laser trabeculoplasty—studies of mechanism of action. *Ophthalmology* 1984; **91:** 1005–10.
18 Alvarado JA. Laser photocoagulators for glaucoma research and therapy. *Arch Ophthalmol* 1984; **102:** 1604–5.
19 Starita RJ, Fellman RL, Spaeth GL, Poryzees E. The effect of repeating full circumference argon laser trabeculoplasty. *Ophthalmic Surg* 1984; **15:** 41–3.
20 Brown SVL, Thomas JV, Simmons RJ. Laser trabeculoplasty re-treatment. *Am J Ophthalmol* 1985; **99:** 8–10.
21 Gaasterland D, Kupfer B. Experimental glaucoma in the rhesus monkey. *Invest Ophthalmol Vis Sci* 1974; **13:** 455–7.
22 Wilensky JT, Jampol LM. Laser therapy for open angle glaucoma. *Ophthalmology* 1981; **88:** 213–7.
23 Pohjanpelto P. Argon laser treatment of the anterior chamber angle for increased intraocular pressure. *Acta Ophthalmol (Kbh)* 1981; **59:** 211–20.
24 Thomas JV, Simmons RJ, Belcher CD. Argon laser trabeculoplasty in the presurigical glaucoma patient. *Ophthalmology* 1981; **89:** 187–97.
25 Krupin T, Kolker AE, Kass MA, Becker, B. Intraocular pressure the day of argon laser trabeculoplasty in primary open angle glaucoma. *Ophthalmology* 1984; **91:** 361–5.
26 Rosenbloom AL, Silverstein JH, Lezotte DC, Richardson K, McCallum M. Limited joint mobility in childhood diabetes mellitus indicates increased risk for microvascular disease. *N Engl J Med* 1981; **305:** 191–4.
27 Knowles B. Joint contractures, waxy skin and control of diabetes. *N Engl J Med* 1981; **305:** 217–8.
28 Levine RL. Lasers and glaucoma. *Ann Ophthalmol* 1984; **16:** 520–1.
29 Nesterov AP, Batmenov YE. Trabecular wall of Schlemm's canal in the early stage of primary open angle glaucoma. *Am J Ophthalmol* 1974; **78:** 639–47.
30 Ellingsen BA, Grant WM. The relationship of pressure and aqueous outflow in enucleated human eyes. *Invest Ophthalmol Vis Sci* 1971; **10:** 430–7.
31 Johnstone MA, Grant WM. Pressure-dependent exchanges in configuration of endothelial tubules of Schlemm's canal. *Am J Ophthalmol* 1973; **75:** 365–83.
32 Grierson I, Lee WR. Changes in monkey outflow apparatus at graded levels of intraocular pressure: a qualitative analysis by light microscopy and scanning electron microscopy. *Exp Eye Res* 1974; **19:** 21–33.
33 Lunde MW. Argon laser trabeculoplasty in pigmentary dispersion syndrome with glaucoma. *Am J Ophthalmol* 1983; **96:** 721–5.
34 Pohjanpelto P. Late results of laser trabeculoplasty for increased intraocular pressure. *Acta Ophthalmol (Kbh)* 1983; **61:** 998–1009.
35 Watson PG, Grierson I. The place of trabeculectomy in the treatment of glaucoma. *Ophthalmology* 1981; **88:** 175–96.

Accepted for publication 20 February 1987.

British Journal of Ophthalmology, 1988, 72, 270–273

Blood groups as genetic markers in glaucoma

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SUMMARY A series of 474 mixed cases of glaucoma was assessed to determine whet
any genetic differences between different types of glaucoma. A careful distinct
between chronic open angle glaucoma (COAG), acute and chronic angle closure gla
hypertension, low tension glaucoma, patients with large cup disc ratios, and va
secondary glaucoma including pseudoexfoliation of the lens capsule, uveitic
glaucoma. Using ABO blood groups, Rhesus groups, ABH secretion or non-
phenylthiourea tasting we identified certain differences. The differences from
significant decrease in Rh-negative patients in chronic closed angle glaucoma ($p<0\cdot$
in ABH secretors in ocular hypertension ($p<0\cdot01$), and fewer HB secretors in patien
($p<0\cdot02$). There was a significant decrease in AH secretors and increase in HB se
pseudoexfoliation with raised intraocular pressure compared with COAG ($p<$
secondary glaucomas as a group compared with COAG ($p<0\cdot01$). Tasters of pheny
more common in traumatic and uveitic glaucoma than in normal controls ($p<0\cdot05$)
suggest that secondary glaucoma develops in different subjects from COAG, whil
develop a rise in intraocular pressure proceed to cupping and field loss if they have a
constitution. The groups of patients are too small for the differences to be of great pr

It has been suggested that the distribution of a number of genetically determined characters may act as markers for glaucoma,[1] particularly open angle glaucoma, which occurs more frequently in families[2] and which is thought to be of multifactorial inheritance.[3] If this is so, then the careful separation of cases of glaucoma secondary to pseudoexfoliation of the lens capsule (PXF), trauma or cyclitis may display these genetic markers more clearly. Further there may be genetic differences between chronic open angle glaucoma (COAG), with cupping and field defects, and ocular hypertension, where cupping and field loss have not developed in spite of raised intraocular pressure. Similarly genetic differences may exist in low tension glaucoma, where cupping and field loss have developed in patients with normal pressure. If such genetic differences do exist, they may have diagnostic and prognostic value.

Most recognisable genetic inheritance in man, if not specifically pathogenetic, concerns blood groups. The relative frequencies of the ABO blood groups, the hereditary presence or absence in the saliva of the individual's ABO blood group an
secretion or non-secretion, and the ab
to taste certain thyroid-inhibiting
thiourea, such as phenylthiourea (PT
ors of genetic associations. The domi
genes responsible for the ability to se
or O antigen in the saliva are not link
genes.[4] Such genetic associations wo
nostic value, particularly if there
between the various types of glaucom
antigens are found in the saliva of se
not present in non-secretors. The a
these antigens is inherited in a
dominant manner and may be associa
diseases.[4]

To investigate these genetic assoc
were investigated in the Glaucoma In
Research Unit during 1983 to 1984,
and rhesus blood groups, ABH sec
tasting status were determined. Part
was paid to precise diagnosis of the ty
so that any specific genetic associa
identified. In particular, secondary g
considered separately, whether due t

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or cyclitis. A distinction was made between COAG with cupping and field loss, ocular hypertension with neither of these, and low tension glaucoma. A group of patients with large cups of the optic disc but no field loss and normal pressure was also examined. Angle closure glaucoma was separated into acute and chronic subgroups.

Materials and methods

In all new patients attending the Glaucoma Investigation and Research Unit during 1983–4 blood grouping was performed for the ABO blood groups and rhesus groups; secretor status was determined[4] and phenylthiourea (1:50 000) tasting was performed.

Patients classified as ocular hypertensive had a pressure greater than 22 mmHg with no field loss or cupping of the optic disc. In chronic open angle glaucoma patients showed a typical field defect and pathological cupping of the optic disc with a pressure greater than 22 mmHg. Patients with low tension glaucoma showed similar field defects and cupping of the optic disc with a pressure which never rose above 22 mmHg. Cases of PXF, traumatic glaucoma, uveitic glaucoma, and acute or chronic angle closure glaucoma showed the typical physical signs of these conditions.

Statistical analysis of the data was by the χ^2 test.

Results

We examined 158 patients with ocular hypertension, 130 with COAG and 53 with low tension glaucoma. We also examined 55 patients with PXF with glaucoma, 14 with PXF with ocular hypertension, nine with PXF with no ocular hypertension, 10 with traumatic glaucoma, 11 with secondary uveitic glaucoma, 20 with acute angle closure glaucoma, 23 with chronic angle closure, and nine with neovascular glaucoma following central retinal vein thrombosis. The results were compared with those from 125 normal, age-matched control subjects and with the blood group distribution in 13 805 blood donors of the Red Cross Blood Bank of Victoria[5] over the same period of time, whose ethnic composition was the same as our group of patients. We examined a further 28 patients with no glaucoma but with cup disc ratio greater than 0·6.

There was no significant difference between our controls and those of the Blood Bank nor between the controls and those without glaucoma but with cup disc ratio greater than 0·6.

BLOOD GROUPS

There were no significant differences between any of the groups studied in the relative frequencies of the ABO blood groups (Table 1). There was also no significant difference in the relative frequency of any of the ABO groups in the 310 patients suffering from glaucoma compared with normal controls ($\chi^2=2{\cdot}76$, 3 DF, $0{\cdot}50>p>0{\cdot}30$). However, there was a significant decrease in the number of Rh-negative patients in chronic angle closure glaucoma compared with acute angle closure glaucoma ($\chi^2=5{\cdot}24$, 1 DF, $p<0{\cdot}05$).

Table 1 *Blood group results*

	A	*B*	*O*	*AB*	*Rh+*	*Rh−*
Normal controls	47	19	54	5	109	16
Red Cross Blood Bank (%)	39	11	46	4	82	18
No glaucoma C/D>0·6	9	5	13	1	25	3
Ocular hypertension (OHT)	73	11	69	5	134	24
Chronic open angle glaucoma	53	12	61	4	113	17
Low tension glaucoma	20	8	21	4	48	5
Pseudoexfoliation with glaucoma	21	7	27	0	48	7
Pseudoexfoliation with OHT	5	5	6	0	14	2
Pseudoexfoliation, no OHT	7	0	2	0	9	0
Traumatic glaucoma	3	2	3	2	9	1
Secondary uveitic glaucoma	3	2	3	2	9	1
Acute angle closure glaucoma	9	2	8	1	14	6
Chronic angle closure glaucoma	13	2	8	0	22	1
Neovascular glaucoma	1	2	5	1	8	1

C/D=cup/disc ratio.

SECRETOR STATUS

The results of secretor status studies are shown in Tables 2 to 4. The secretors are compared with nonsecretors in Table 2. There were fewer secretors in patients with ocular hypertension than in our normal controls ($\chi^2=5{\cdot}68$, 1 DF, $p<0{\cdot}02$) and the Blood Bank controls ($\chi^2=12{\cdot}08$, 1 DF, $p<0{\cdot}01$). There were also significantly fewer secretors among patients with ocular hypertension than among those with COAG

Table 2 *Secretor status results*

	Secretors *(number of patients)*	*Non-secretors*
Normal controls	99	23
Red Cross Blood Bank (%)	80	20
No glaucoma C/D>0·6	27	5
Ocular hypertension (OHT)	107*	49
Chronic open angle glaucoma	103	26
Low tension glaucoma	37	11
Pseudoexfoliation with glaucoma	44	10
Pseudoexfoliation with OHT	14	2
Pseudoexfoliation, no OHT	6	3
Traumatic glaucoma	9	1
Secondary uveitic glaucoma	11	1
Acute angle closure glaucoma	11	8
Chronic angle closure glaucoma	18	5
Neovascular glaucoma	6	3

*Significant to $p<0{\cdot}01$ compared with normal controls ($\chi^2=5{\cdot}68$, 1 DF, $p<0{\cdot}02$) and Blood Bank controls ($\chi^2=12{\cdot}08$, 1 DF, $p<0{\cdot}01$).

Table 3 *Secretor group results*

	Secretor group (number of patients)						
	AH	*H*	*HB*	*AB*	*ABH*	*A*	*B*
Normal controls	38	39	18	0	4	0	0
No glaucoma C/D>0·6	7	11	5	0	0	0	0
Ocular hypertension (OHT)	51	43	10	0	2	0	1
Chronic open angle glaucoma	44	48	5*	0	3	0	3
Low tension glaucoma	15	17	4	1	0	0	0
Pseudoexfoliation with glaucoma	12	24	6	1	0	1	0
Pseudoexfoliation with OHT	4	4	5	0	1	0	0
Pseudoexfoliation, no OHT	4	2	0	0	0	0	0
Traumatic glaucoma	3	2	2	0	2	0	0
Secondary uveitic glaucoma	3	2	4	0	2	0	0
Acute angle closure glaucoma	4	5	2	0	0	0	0
Chronic angle closure glaucoma	9	7	2	0	0	0	0
Neovascular glaucoma	1	2	1	1	0	0	1

*Significant compared with normal (χ^2=11·78, 4 DF, p<0·02).

(χ^2=4·65, 1 DF, p<0·05) and all the patients with glaucoma considered as a whole (χ^2=5·58, 1 DF, p<0·02).

The secretor subgroups are shown in Table 3. There were significantly fewer HB secretors in patients with COAG than the normal controls (χ^2= 11·78, 4 DF, p<0·02). Ocular hypertensives had an incidence of HB secretors intermediate between normal patients and those with COAG, but this difference was not statistically significant.

The patients with PXF and raised intraocular pressure included fewer AH secretors and more HB secretors than those with COAG (χ^2=8·35, 1 DF, p<0·01) (Table 4).

The secretor status of secondary glaucoma also differed from COAG, with an increase in HB and decrease in AH secretors in secondary glaucoma, whether angle closure glaucomas were included (χ^2= 20·04, 7 DF, p<0·01) or not (χ^2=31·89, 7 DF, p<0·01).

Comparing all the cases of glaucoma as a whole, we found no significant difference from the controls in the relative frequency of ABH secretors and non-secretors (χ^2=0·34, 1 DF, 0·70>p>0·50).

Table 4 *Secretor profiles for pseudoexfoliative glaucoma (PXFG) and pseudoexfoliatives with ocular hypertension (PXFOHT) compared with chronic open angle glaucoma (COAG)*

	Secretor group (number of patients)						
	AH	*H*	*HB*	*AB*	*ABH*	*A*	*B*
PXFG and PXFOHT (58)	16	28	11	1	1	1	0
COAG (103)	44	48	5	0	3	0	3

Significant difference in AH and AB secretors in PXFG and PXFOHT compared with COAG (χ^2=8·35, 1 DF, p<0·01).

Table 5 *Taster status results*

	Tasters	*Non-tasters*
Normal controls	44	76
No glaucoma C/D>0·6	8	17
Ocular hypertension (OHT)	46	105
Chronic open angle glaucoma	43	82
Low tension glaucoma	17	31
Pseudoexfoliation with glaucoma	16	39
Pseudoexfoliation with OHT	5	7
Pseudoexfoliation, no OHT	2	7
Traumatic glaucoma	6*	3
Secondary uveitic glaucoma	6†	3
Acute angle closure glaucoma	5	15
Chronic angle closure glaucoma	12	9
Neovascular glaucoma	4	5

*Significant compared with normal controls (χ^2=24·8, 1 DF, p<0·01). †Significant compared with normal controls (χ^2=4·8, 1 DF, 0·05>p>0·02).

TASTER STATUS

The results are shown in Table 5. Patients who were tasters were significantly more common among those with traumatic glaucoma than among normal controls (χ^2=24·8, 1 DF, p<0·01) and secondary uveitic glaucoma (χ^2=4·8, 1 DF, 0·05>p>0·02).

Discussion

This study supports the presence of certain genetic markers which distinguish some patients with COAG from normal controls and from patients with ocular hypertension. Thus patients with COAG had a significantly lower incidence of HB secretors than normal controls, with an incidence for ocular hypertensives intermediate between normal subjects and those with COAG. There were fewer ABH secretors in ocular hypertension than in patients with COAG and also fewer than in the normal controls.

Therefore normal patients who are HB secretors are much less likely to develop glaucoma. If such patients develop ocular hypertension, they are less likely than other patients to proceed to the development of cupping and field loss. The lower incidence of ABH secretors in ocular hypertension compared with COAG and normal persons suggests there is a genetic difference between some patients who develop ocular hypertension and do not go on to cupping and field loss and those who do.

The patients with PXF and raised intraocular pressure had a lower incidence of AH secretors and a higher incidence of HB secretors than those with COAG, their incidence resembling that of normal patients. This is compatible with previous work which suggested that the rise in pressure in PXF is secondary to the presence of the PXF material occurring in otherwise normal eyes not predisposed to glaucoma.[6] Further, in cases of unilateral PXF with a raised intraocular pressure a significant difference in cup disc ratio between affected and unaffected eyes has been reported; the increased cupping followed the development of raised intraocular pressure due to deposition of PXF.[7]

When all cases of secondary glaucoma as a group were compared with those with COAG, there was also a higher frequency of HB secretors and a lower frequency in AH secretors whether angle closure glaucomas were included or not. This confirms a genetic difference between some patients with COAG and those with secondary glaucoma like that noted for PXF.

Of less importance—patients who were tasters of phenylthiourea were more common among patients with traumatic and secondary uveitic glaucomas than among normal people. It has previously been noted that the fellow eyes of eyes with traumatic glaucoma have some increase of pressure, and therefore some patients are more likely to develop a rise in pressure after severe contusion injury,[8 9] being different from the normal population.

We observed an association between ocular hypertension and non-secretion of ABH but not between COAG and non-secretion of ABH, although an association between non-secretors of ABH and primary glaucoma (open angle and narrow angle) has been reported from India.[10]

The familial incidence of chronic simple glaucoma and angle closure glaucoma has been emphasised by Miller,[11] and other workers have reported increased group A in open angle glaucoma,[12] of group O in congestive glaucoma,[13] and of rhesus-positivity in open angle glaucoma,[14] but we did not confirm a statistical association between the ABO blood groups and these glaucomas. Nor did we substantiate PTC tasting status as a marker for glaucoma, as shown by a previously reported[15] raised incidence of non-tasters among patients with primary chronic simple glaucoma or tasters in patients with closed angle glaucoma.

Our failure to confirm some previously reported work emphasises that much of the work done on the genetic status of patients with glaucoma is conflicting. It should be remembered that statistical analysis indicates degrees of probability, and there may be genetic differences between population groups making comparison difficult.

We believe that the present study defines different types of glaucoma more carefully and may therefore be more likely to detect genetic differences, but few were found. The study does suggest that the secretor status of patients with ocular hypertension may be helpful in determining which patients are more likely to progress to glaucoma. Unfortunately only a small proportion of patients are HB secretors, so the genetic markers we have described are only of limited usefulness in predicting which ocular hypertensive patients are likely to develop cupping and field loss. Perhaps more sophisticated studies of blood groups and subgroups will refine these tests further and make more comprehensive and precise prediction possible.

This work was carried out under Research Project 20 of the Royal Victorian Eye and Ear Hospital. We thank Dr Kathy McGrath, Assistant Director of the Red Cross Blood Bank of Victoria, and Dr John Weiner, Director of Pathology the Royal Victorian Eye and Ear Hospital, for their help. This work would not have been possible without the assistance of Sister M Maher and the staff of the Number 2 Eye Outpatients of the Royal Victorian Eye and Ear Hospital.

References

1 Anonymous. Genetic associations of glaucoma. (Editorial). *Br J Ophthalmol* 1980; 64: 225–6.
2 Shin DH, Becker B, Kolker AE. Family history in primary open-angle glaucoma. *Arch Ophthalmol* 1977; 95: 598–600.
3 Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. 1. The demonstration of 3 levels of response. *Invest Ophthalmol Vis Sci* 1965; 4: 187–97.
4 Race RR, Sanger R. *Blood groups in man*. 6th ed. Oxford: Blackwell, 1975; 9: 321–3.
5 McGrath K. *Blood group distribution in donor population 1983, 1986*. Blood Bank of Victoria 1983, 1986.
6 Gillies WE. Corticosteroid-induced ocular hypertension in pseudo-exfoliation of lens capsule. *Am J Ophthalmol* 1970; 70: 90–5.
7 Gillies WE, West RH. Unilateral pseudo-exfoliation, ocular hypertension and the cup disc ratio. *Aust J Ophthalmol* 1981; 9: 321–3.
8 Gillies WE. Traumatic glaucoma. *Trans Ophthalmol Soc Aust* 1967; 26: 54–8.
9 Armaly MF. Inheritance of dexamethasone hypertension and glaucoma. *Arch Ophthalmol* 1967; 77: 747–51.
10 Garg MP, Pahwa JM. Primary glaucoma and blood groups. *J All India Ophthalmol Soc* 1965; 13: 127–9.
11 Miller SJH. Genetic aspects of glaucoma. *Trans Ophthalmol Soc UK* 1966; 86: 425–34.
12 Arezzi R. Report on the ABO blood-group system and chronic simple glaucoma. *Minerva Oftalmol* 1976; 18: 77–81.
13 Kubickova A, Kloucek F, Kraus H, Dvorakova M. ABO blood groups, secretory behaviour and PTC tasting of glaucoma patients. *Klin Monatsbl Augenheilkd* 1972; 161: 32–5.
14 David R, Jenkins T. Genetic markers in glaucoma. *Br J Ophthalmol* 1980; 64: 227–31.
15 Mourant AE, Kopec AC, Domaniewska-Sobczak K. *Blood groups and diseases*. Oxford: Oxford University Press, 1978: 250–1.

Accepted for publication 10 February 1987.

British Journal of Ophthalmology, 1988, 72, 274–277

The evaluation of corneal endothelial permeability in PERK study patients*

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SUMMARY Sixteen patients enrolled in the PERK study were evaluated by fluorophotometry 24 hours or six months following radial keratotomy. A comparison of eyes operated and not operated upon showed that endothelial permeability was not significantly altered 24 hours and six months after surgery. Aqueous humour flow rates and anterior chamber elimination coefficients were significantly higher 24 hours after surgery in the eyes operated on than in those not operated on. Six months after surgery there was no longer a significant difference in these factors. The increase in aqueous humour flow rates 24 hours after surgery may represent a subclinical breakdown in the blood-aqueous barrier.

Anterior radial keratotomy, a surgical procedure for the correction of myopia, is at present being evaluated by the PERK (Prospective Evaluation of Radial Keratotomy) study, to determine the predictability, safety, and short and long term effects of the surgery. The operation, as originally performed by Sato,[1] consisted of anterior and posterior radial corneal incisions. Unfortunately, as many as 75% of his patients developed bullous keratopathy 10–15 years after surgery.[2 3] Because of this severe complication, the surgery was altered by Fyodorov and Durnev[4] to consist of only anterior radial corneal incisions. We carried out a study to evaluate the effect of anterior radial keratotomy, performed according to the PERK surgical protocol,[5] on endothelial cell function, measured by fluorophotometry.

Subjects and methods

Seventeen of the 38 patients enrolled in the PERK study[5] at the Mount Sinai Medical Center between December 1982 and October 1983 agreed to undergo fluorophotometry. One patient was excluded from the study owing to difficulty in data interpretation. Eleven patients were examined by fluorophotometry 24 hours after surgery and five patients six months after surgery.

Six of the patients examined 24 hours after surgery were male and five were female. Six had the right eye operated on, five the left eye. The patients were between 22 and 46 years of age, average 29 (SD 8) years. Preoperative spherical equivalent varied between −2·25 dioptres and −4·75 dioptres.

Five patients underwent fluorophotometry six months after radial keratotomy, three male and two female. Two patients had the right eye operated on, three the left eye. These patients were between 22 and 38 years of age, average 32 (SD 7) years. The preoperative spherical equivalent varied between −2·00 dioptres and −8·00 dioptres.

Radial keratotomy was performed by one of us (SAO) according to the PERK surgical protocol.[5] It consisted of eight radial anterior corneal incisions to 100% of the depth of the thinnest paracentral area, measured with an ultrasonic pachymeter. A central 3 to 4 mm optical clear zone was left untouched, depending on the preoperative refraction, and the incisions did not extend past the limbus. In no case was the anterior chamber entered during surgery.

Fluorophotometry was performed with a slit-lamp fluorophotometer. Fluorescein sodium 0·25% and 0·4% benoxinate hydrochloride (Fluress, Barnes-Hind) was applied topically to both eyes, one drop every three minutes for 10 doses. Measurements of

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*This study was presented in part at the Association for Research in Vision and Ophthalmology Meeting, Sarasota, Florida, 4 May, 1984.

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fluorescence in the cornea and in the anterior chamber were begun two and a half hours after fluorescein application and continued every 20 minutes for four hours. The unoperated eye served as the control eye, and was compared with the operated eye in these experiments.

The data were analysed by a computerised model according to the method of Jones and Maurice[6] on the assumption of an anterior chamber volume of 175 μl and a corneal volume of 70 μl. K_o, the anterior chamber elimination coefficient; K_{cac}, the cornea-to-aqueous transfer coefficient; K_{aac}, the corneal transfer coefficient referred to the volume of the anterior chamber; and F, the aqueous humour flow rate, were calculated. Corneal endothelial permeability was calculated on the assumption of a corneal stromal thickness of 0·47 mm. The unoperated control eyes were compared with the operated eyes for statistical analysis.

Gross outflow facility was measured on four patients at 24 hours and at one year after the initial radial keratotomy on the second eye, and on one patient at 24 hours and at one year after the second procedure on the second eye. Outflow facility was measured for four minutes on each eye with an electronic Schiøtz tonometer. In three of these five patients the intraocular pressure was measured with a Goldmann applanation tonometer 24 hours and one year after surgery. The scleral rigidity in these three patients was calculated 24 hours and one year after surgery by the Friedenwald nomogram, the applanation intraocular pressure, and the initial intraocular pressure from the tonographic tracing. For statistical analysis the most recently operated eye was compared with the eye which had undergone surgery one year previously.

The paired *t* test was used to compare the treated and contralateral control eyes.

Results

Twenty-four hours after radial keratotomy was performed on 11 patients there was no significant difference in K_{cac}, K_{aac}, and the endothelial permeability in a comparison of operated and unoperated eyes (Table 1). K_o was significantly ($p<0·001$) higher in the operated eye, 2·2±0·6 min^{-1} (mean±SD), compared with the unoperated eye, 1·5±0·6 min^{-1}. F was significantly ($p<0·001$) higher in the operated eye, 3·9±1·0 μl/min, compared with the unoperated eye, 2·6±1·1 μl/min.

Six months after radial keratotomy there was no significant difference in K_{cac}, K_{aac}, endothelial permeability, K_o, or F, in a comparison of operated and unoperated eyes in five patients (Table 2).

Table 1 *Fluorophotometry performed on 11 patients 24 hours after radial keratotomy*

	K_{cac} 10^{-3} min^{-1}	*K_{aac} 10^{-3} min^{-1}*	*Endothelial permeability 10^{-4} cm/min*	*K_o 10^{-2} min*	*F μl/min*
Operated	4·3 ±0·9†	1·7 ±0·4	3·2 ±0·7	2·2* ±0·6	3·9* ±1·0
Unoperated	4·0 ±1·3	1·6 ±0·5	2·9 ±1·0	1·5 ±0·6	2·6 ±1·1

*Significant difference between operated and unoperated eyes, paired *t* test, $p<0·001$. †Mean±SD.

Table 2 *Fluorophotometry performed on five patients six months after radial keratotomy*

	K_{cac} 10^{-3} min^{-1}	*K_{aac} 10^{-1} min^{-1}*	*Endothelial permeability 10^{-4} cm/min*	*K_o 10^{-2} min*	*F μl/min*
Operated	4·0 ±1·1†	1·6 ±0·4	2·9 ±0·8	2·0 ±0·6	3·5 ±1·0
Unoperated	4·0 ±1·5	1·6 ±0·6	2·9 ±1·1	2·1 ±0·7	3·7 ±1·5

†Mean±SD.

Gross outflow facility was significantly ($p<0·05$) higher in five patients in the newly operated eye, 0·55±0·09 (mean μl/min mmHg±SD), compared with the eye which had been operated on the year before, 0·39±0·10 μl/min mmHg. Intraocular pressure, obtained from the tonograms, was not significantly different in a comparison of the recently operated and the previously operated eyes respectively, 12·5±3·5 (mean mmHg±SD) and 14·8±3·2 mmHg. One year after surgery on the second eye the outflow facility was similar, 0·30±0·09 μl/min mmHg±SD in the most recently operated eye, and 0·31±0·13 μl/min mmHg in the contralateral eye. The intraocular pressure measured with a Goldmann applanation tonometer was not significantly different in the treated eyes 12·0±1·2 mmHg and the control eyes 13·0±3·7 mmHg one year after surgery. The ocular rigidity in three of these patients was similar, 0·031±0·015 (±SD) in the recently operated eye and 0·028±0·007 in the contralateral eye 24 hours postoperatively, and 0·028±0·004 and 0·026±0·003 at one year in the most recently operated eye and in the contralateral eye, respectively.

Discussion

Endothelial permeability, as measured by fluorophotometry, was unaltered at 24 hours and six months after radial keratotomy. Our results on endothelial permeability are similar to those of Hull *et al.*[7] in the rabbit. This group assessed endothelial permeability by measuring the flux of tritiated inulin and carbon-14 labelled dextran, and by fluorophotometry. They did not demonstrate a significant alteration in endothelial permeability to any of these three substances between 24 hours and 10 weeks after radial keratotomy. Rabbit corneal endothelium responds to injury by proliferation,[8] in contrast to human corneal endothelium. Hull used the same inulin and dextran radioactive flux technique in the owl monkey[9] and demonstrated a transient increase in endothelial permeability to inulin in the operated eyes two days after radial keratotomy, with a return to levels comparable to those of the unoperated eyes four weeks after surgery. Dextran permeability was unaltered two days and four weeks following the procedure. The monkey corneal endothelium showed a transient increase in permeability to the smaller 1·4 nm inulin molecule, but not to the larger 3·8 nm dextran molecule. The fluorescein molecule measures 0·5 nm, but fluorophotometry was not performed on these monkeys. Recently Beatty and Smith[10] found a persistent increase in corneal endothelial permeability to fluorescein during the first three months following radial keratotomy in the owl monkey. Corneal endothelial permeability in these animals was not increased from six months to two years following surgery.

K_o, the transfer coefficient of aqueous out of the eye, was significantly ($p<0{\cdot}001$) increased 24 hours after surgery in our studies. This transient increase in K_o may be due to a temporary alteration in the configuration of the anterior chamber, resulting in a temporary increase in outflow facility. Zimmerman *et al.*[11] demonstrated a decrease in outflow facility following removal of through-and-through sutures from penetrating keratoplasties in eye bank eyes. Gross outflow facility was significantly ($p<0{\cdot}05$) higher in five patients in the newly operated eye, 0·55±0·09 (mean µl/min mmHg±SD), compared with the eye which had been operated on the year before, 0·39±0·10 µl/min mmHg±SD. Intraocular pressure, obtained from the tonograms, was not significantly different in comparisons of the recently operated and the previously operated eyes, 12·5±3·5 (mean mmHg±SD) and 14·8±3·2 mmHg respectively. The coefficient of ocular rigidity was similar in the eyes examined 24 hours after surgery and the contralateral eyes. One year after surgery the outflow facility was no longer significantly different in treated and control eyes. The intraocular pressure and the coefficient of ocular rigidity were also similar one year after surgery.

The increase in aqueous humour flow rates in the operated eye 24 hours after surgery may represent a real increase. More probably it represents a subclinical breakdown in the blood-aqueous barrier. Clinically these patients did not show cells or flare on slit-lamp examination postoperatively. A real increase in aqueous humour flow is difficult to explain after radial keratotomy. Hull *et al.*[7] reported a decrease in aqueous humour flow rates, measured by fluorophotometry, in rabbits one and 10 weeks after radial keratotomy.

The stability of endothelial permeability to fluorescein at 24 hours and six months after radial keratotomy in humans is encouraging. Two factors must be emphasised. Firstly, fluorophotometry is a mass measurement of corneal endothelial function; very small variations in permeability, or localised alterations in endothelial cell function, may not become apparent with this technique. Secondly, six months is a relatively short-term evaluation of endothelial function. The corneas Sato operated on did not show bullous keratopathy until 10 or more years after surgery,[2] and he was directly injuring the endothelial cells with the posterior incisions.

Other methods of evaluating corneal endothelium after radial keratotomy have included specular microscopy. Studies in animal models (monkeys) suggest cell loss of 10–15% in the early postoperative period, which does not appear to progress over a 1–2 year follow-up period.[12,13] Several groups have looked at endothelial cell counts in humans and have found 0 to 10% cell loss in the central cornea, the amount depending on the study. Studies of the peripheral cornea, directly under the incisions, have also not demonstrated significant cell loss or alteration in the first year after surgery.[14]

Longer periods of endothelial evaluation postoperatively and more sensitive methods of evaluation would be helpful in determining alterations in corneal endothelial cell function after radial keratotomy.

This work was supported in part by NEI 5-RO1-EY03751 and Y-01867, and an unrestricted grant from Research to Prevent Blindness, Inc., New York.

References

1 Sato T, Akiyama K, Shibata H. A new surgical approach to myopia. *Am J Ophthalmol* 1953; **36:** 823–9.

2 Kanai A, Yamaguchi T, Yajima Y. The fine structure of bullous keratopathy after anteroposterior incision of the cornea for myopia. *Folia Ophthalmol Jpn* 1979; **30:** 841–9.

3 Yamaguchi T, Kanai A, Tanaka M. Bullous keratopathy after anterior/posterior radial keratotomy for myopia and myopic astigmatism. *Am J Ophthalmol* 1982; **93:** 600–6.

4 Fyodorov SN, Durnev VV. Anterior keratotomy method application with the purpose of surgical correction of myopia. *Pressing problems of ophthalmosurgery.* Moscow Press, 1977.

5 Waring GO, Moffitt SD, Gelender H, *et al.* Rationale for design of the national eye institute prospective evaluation of radial keratotomy (PERK) study. *Ophthalmology* 1983; **90:** 40–58.

6 Jones RF, Maurice DM. New methods of measuring the rate of aqueous flow in man with fluorescein. *Exp Eye Res* 1966; **5:** 208–20.

7 Hull DS, Farkas S, Green K, Laughter L, Elijah D, Bowman K. Radial keratotomy effect on cornea and aqueous humor physiology in the rabbit. *Arch Ophthalmol* 1983; **101:** 479–81.

8 Van Horn DL, Sendele DD, Seidman S. Regenerative capacity of the corneal endothelium in rabbit and cat. *Invest Ophthalmol Vis Sci* 1977; **16:** 597–613.

9 Hull DS, Farkas S, Green K, Laughter L, Bowman K. Radial keratotomy and corneal permeability in owl monkey. *Acta Ophthalmol (Kbh)* 1983; **61:** 240–9.

10 Beatty RF, Smith RE. Corneal endothelial cell permeability to fluorescein following radial keratotomy in owl monkeys. *Invest Ophthalmol Vis Sci* 1986; **27** (suppl): 62.

11 Zimmerman TJ, Krupin T, Grodzki W, Waltman SR. The effect of suture depth on outflow facility in penetrating keratoplasty. *Arch Ophthalmol* 1978; **96:** 505–6.

12 Yamaguchi T, Asbell PA, Ostrick M, Safir A, Kissling GE, Kaufman HE. Endothelial damage in monkeys after radial keratometry performed with a diamond blade. *Arch Ophthalmol* 1984; **102:** 765–9.

13 Dunn S, Jester JV, Arthur J, Smith RE. Endothelial cell loss following radial keratometry in a primate model. *Arch Ophthalmol* 1984; **102:** 1666–70.

14 Asbell PA, Obstbaum S, Justin N. Peripheral corneal endothelial evaluation post radial keratometry in PERK patients. *Ophthalmology* 1984; **91** (suppl): 122.

Accepted for publication 20 February 1987.

British Journal of Ophthalmology, 1988, **72**, 278–283

Experimental suprachoroidal plombage with a urethane based hydrophilic polymer

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SUMMARY Small portions of dehydrated hydrophilic polymer (HPU 90, Smith and Nephew) have been inserted into the suprachoroidal space in rabbits to investigate the possible use of suprachoroidal plombage in retinal detachment surgery. As it hydrates, the material causes a pronounced elevation of choroid and retina, and the implants have been well tolerated for periods of up to one year in experimental animals. The implant slowly breaks down and stimulates a simple macrophagic reaction: fibrosis in the overlying choroid is associated with ischaemic gliosis and chorioretinal fusion.

Localised indentation of the wall of the globe has an accepted role in the treatment of retinal detachment. The main function of such an indent is thought to be approximation of the choroid and retinal pigment epithelium (RPE) to the area of retina affected by a retinal hole. This allows the edges of the hole to be sealed on to the RPE and choroid by the induction of a localised inflammatory reaction by cyrotherapy, diathermy, or other means.

There are disadvantages in episcleral or intrascleral plombage. Distortion of the globe is a necessary result of the operation and may give rise to refractive problems or interfere with the action of an extraocular muscle, leading to diplopia. Extrusion of episcleral onlays is not an uncommon occurrence.

Redmond Smith in 1952[1] suggested the use of suprachoroidal air as a way of achieving temporary choroidal elevation in retinal detachment surgery, but the technique was not widely adopted. One of us (WSF) investigated the use of suprachoroidal gelatin at that time, but preliminary experiments were not successful, mainly because it was found impossible to generate a localised indentation with this material. The advent of hydrophilic polymers offered the possibility of inserting a small portion of dehydrated polymer into the suprachoroidal space, relying on its subsequent hydration to cause a suitable elevation of the choroid.

This paper reports the results of experiments to investigate whether a hydrophilic polymer could be used for suprachoroidal plombage in experimental animals and to investigate the tissue response to see how well it would be tolerated.

Materials and methods

The material tested, HPU 90, was one of a series of hydrophilic urethane based polymers supplied for experimental purposes by Smith and Nephew. Samples were provided which in the hydrated state contained 85, 90, or 95% water. In the hydrated state all were translucent and of a soft, slightly elastic consistency. Dehydrated, they were firm and rigid.

STERILISATION OF POLYMER

Initial attempts to sterilise the material with ethylene oxide led to an unacceptable uveitis when the polymer was subsequently inserted into the eye, probably because the toxic ethylene oxide was retained in the polymer. Sterilisation with gamma radiation was found to cause degradation of the polymer, making it unsuitable for the purpose for which we intended to use it. Eventually the following method of sterilising the polymer was found satisfactory. Portions of hydrated (85% water content) polymer, 3 mm×1 mm×1 mm were continuously irrigated in distilled water for 24 hours to remove any leachables. The washed pieces of polymer were next placed in glass tubes sealed at either end with cotton-wool plugs. The portions of polymer in the glass tubing were autoclaved at 134°C for seven minutes and subsequently dehydrated by being exposed to a current of dry sterile air drawn through the tubes via micropore filters type Millex-GS 0·22 μm for a

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period of 12 hours. When dehydration was complete, one end of the tube was sealed and the other left sealed by the micropore filter.

EXPERIMENTAL METHOD

The experimental animals were Dutch pigmented rabbits of 1·9–2·9 kg body weight. The animals were anaesthetised with intramuscular chlorpromazine (*BP*) (25 mg/ml, 0·5 ml/kg body weight) and intramuscular ketamine hydrochloride (50 mg/ml, 1 ml/kg). The conjunctiva in the upper temporal quadrant of one eye of each animal was incised and a 3 mm circumferential scleral incision made as posteriorly as was conveniently possible. The scleral incision was carried down to the suprachoroidal space, and an iris repositor was used to separate the choroid from the sclera just posterior to the incision. Through the scleral incision a portion of dehydrated polymer was inserted into the suprachoroidal space, care being taken not to damage the underlying choroid. The scleral incision was sutured by one or two 8/0 virgin silk sutures. Topical gentamicin was instilled and the conjunctiva closed with one catgut suture.

HISTOLOGICAL TECHNIQUE

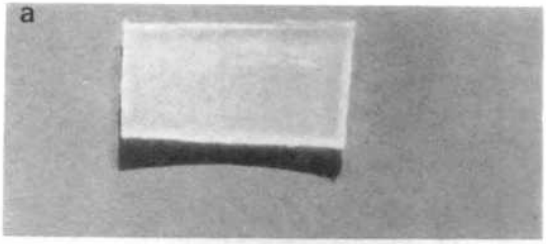
The animals were killed at various time intervals after insertion of the polymer and the eyes enucleated for histological examination, the unoperated eye being used as a control. Enucleated eyes were fixed in glutaraldehyde after a small incision had been made into the vitreous cavity through the pars plana to improve retinal fixation.

The eyes were examined macroscopically and photographed. Blocks were taken from the centre of the specimen, through the pupil and the optic nerve, across the centre of the implant, and were processed routinely for paraffin histology. Sections were stained with haematoxylin and eosin (H and E), periodic acid Schiff (PAS), Bodian, Loyez, and Prussian blue for iron.

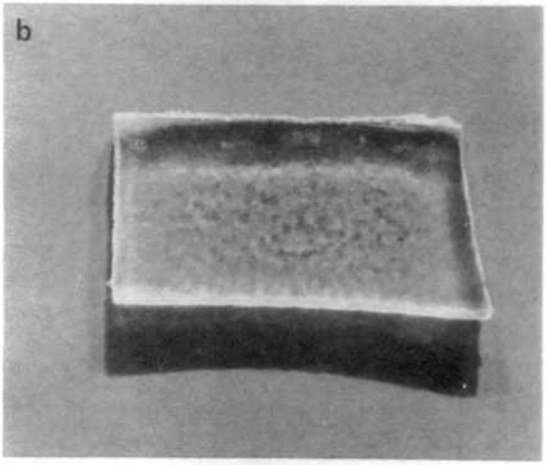
Tissue from selected eyes was postfixed with osmium tetroxide, dehydrated in alcohol, and embedded in Araldite for examination by transmission electron microscopy.

Results

The swelling characteristics of the polymer were tested in vitro by measuring the change in volume against time when a dehydrated portion of polymer was immersed in normal saline. Relative volume changes were assessed from measurements of the linear dimensions of the polymer sample by observing through a light microscope with an eyepiece graticule during hydration. The simple product of linear dimensions was taken rather than attempting to account for irregularities of the specimen. The volume change with time is shown in Figs. 1 and 2, where it can be seen that hydration increased the volume to about 10 times that of the dehydrated state.



Dehydrated Polymer



Hydrated Polymer

Fig. 1 *Photographs of* (a) *dehydrated and* (b) *hydrated HPU 90 hydrophilic polymer to illustrate change in volume on hydration.*

SURGICAL RESULTS

No great difficulty was experienced in inserting the dehydrated polymer into the suprachoroidal space. The material is rigid and easily handled when dehydrated, but if unsuccessful attempts are made to introduce it into the suprachoroidal space it rapidly starts to hydrate and quickly becomes pliable and slippery. It was found important to insert the material in one movement through the scleral incision and suture the incision quickly before significant hydration of the implant had occurred.

The material was inserted in nine rabbit eyes, and in none was there any evidence of immediate or delayed inflammation. Animals were killed for histological examination at time intervals after insertion of

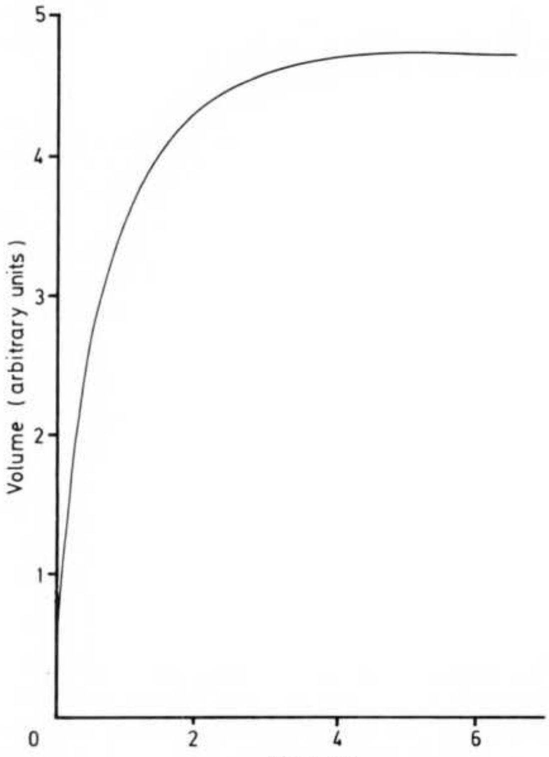


Fig. 2 *Change in volume versus time when a dehydrated portion of HPU 90 polymer is rehydrated* in vitro.

the polymer of one to two hours (four eyes), two weeks, two months, five months, 10 months, and 13 months.

Examination of the eyes immediately after surgery (Fig. 3) showed a localised elevation of choroid and retina which increased in size and depth over a period of two hours or so (Fig. 4). The rate of increase in size was established in one case by serial photography and measurements of height and breadth of the indent. The rate of increase in area of the indent appeared similar to that established for the isolated polymer in vitro. The only change noted in the appearance of the fundus over the months subsequent to the insertion of the polymer was a tendency for the development of a pigmentary disturbance in the region of the implant in two animals (Fig. 5) and a loss of pigment over the implant in another, so that a clear view of the sclera could be obtained through the implant. In one animal the height of the indent decreased after 10 months and by a year after insertion was almost flat (Figs. 6a, b).

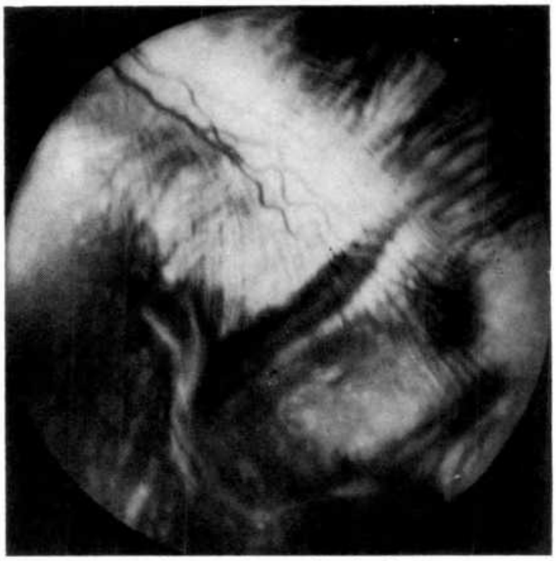


Fig. 3 *Fundus photograph immediately after insertion of dehydrated HPU 90 into the suprachoroid to show localised elevation of choroid and retina.*

HISTOLOGY

On macroscopic examination all specimens of the eyes were free from significant inflammation in either anterior or posterior segment. The position of the implant was marked by a smooth localised elevation of the choroid and retina (Fig. 7). Transection of the implant revealed an empty space with choroid and retina elevated over it (Fig. 8). Histological examination of the tissues in the region of the implant showed a large empty space marking the site of the polymer

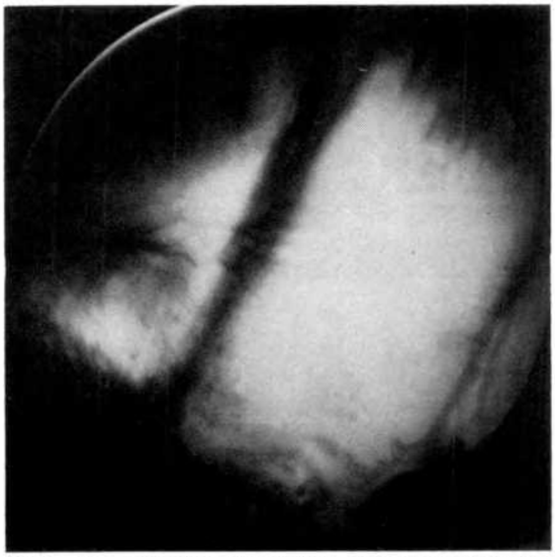


Fig. 4 *Same eye as Fig. 3 two hours later to show increase in the size of the indent.*

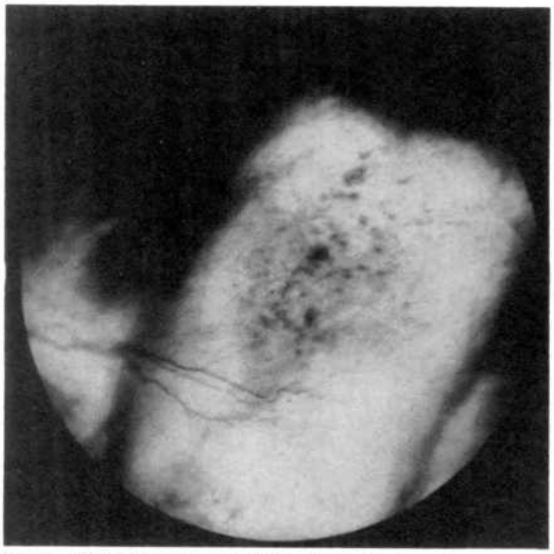


Fig. 5 *Pigmentation over the implanted polymer in an eye in which the polymer had been present for eight weeks.*

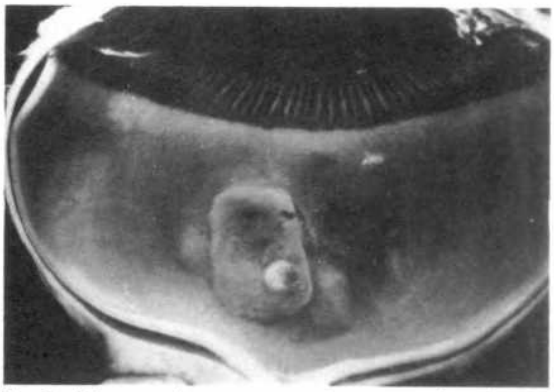


Fig. 7 *Macroscopic appaearance of an eye enucleated after containing a suprachoroidal implant for 14 days. The position of the implant is marked by a localised elevation of choroid and retina.*

and overlying this a thinned choroid and intact but usually depigmented RPE and atrophic retina (Fig. 9).

In four globes in which the implant was in situ for 1–2 hours there was minor subretinal haemorrhage, with preservation of retinal architecture. The implant was located in the suprachoroidal space, and the overlying choroid was thinned. In two eyes there was a low grade polymorphonuclear leucocytic reaction in the adjacent choroid. The RPE in two eyes was thinned or absent in some sections.

Four globes in which the implant had been present for 2, 8, or 10 months showed similar changes in that the implant space contained granular eosinophilic material which was surrounded by a band of foamy macrophages (Figs. 10a, b). The choroid was replaced by a band of fibrous tissue in which there was chorioretinal fusion and the RPE appeared progressively more atrophic in the longer experiments. At two weeks there was atrophy and gliosis of the retina over the centre of the implant with RPE

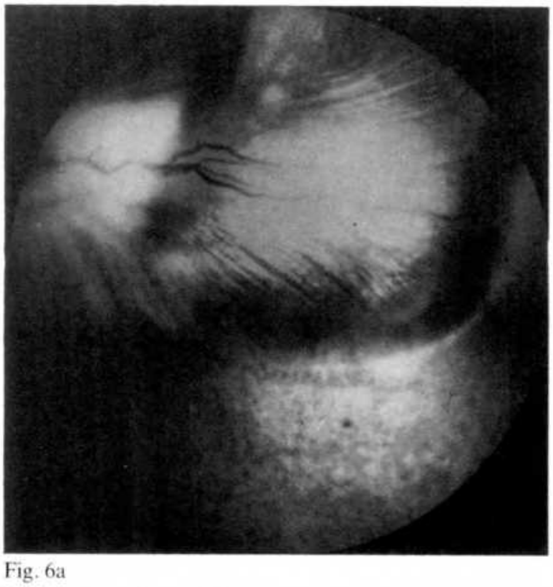


Fig. 6a

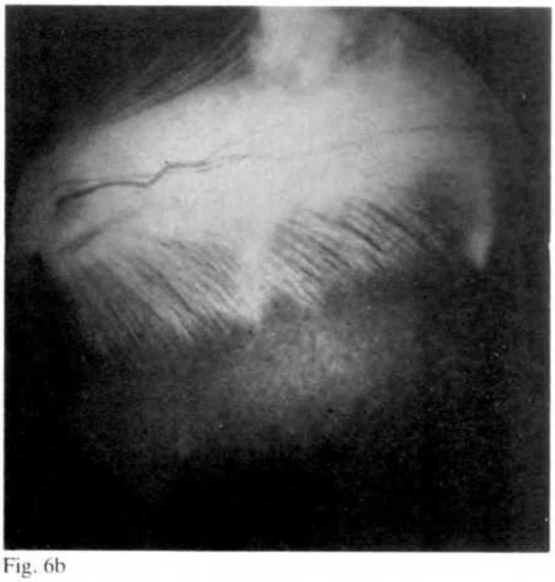


Fig. 6b

Fig. 6 *Suprachoroidal implant at two months* (a) *and 10months* (b). *Height of the indent is decreasing.*

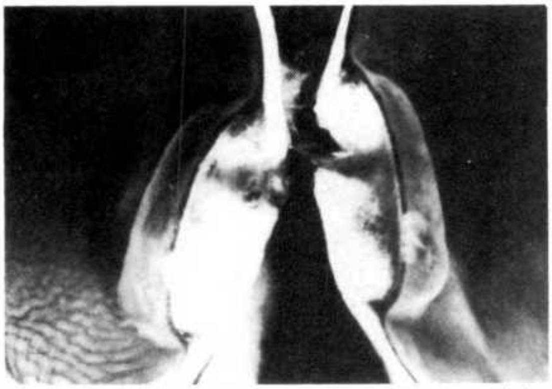


Fig. 8 *Transection of the implant shown in Fig. 7 reveals the position of the implant as an empty space with choroid and retina elevated over it.*

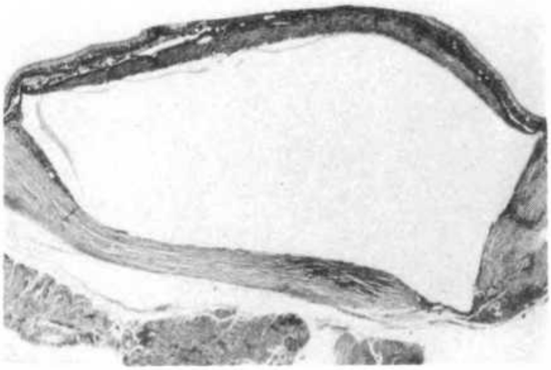


Fig. 9 *Histology of eye shown in Figs. 7 and 8. The implant is covered internally by thinned choroid, RPE, and atrophic retina. There is no significant inflammatory reaction.* ×26.

migration. The surrounding photoreceptor layer showed atrophy with reactionary proliferation of the RPE. In the 10-week specimen there was extensive retinal atrophy which extended up to 4 mm from the site of the implant. In each specimen the sclera beneath the implant showed a giant-cell granulomatous reaction to suture material, and in eyes in which the implant had been present for longer periods there was scleral thinning.

The globe removed at 10 months following implantation was different in that the inner retinal architecture was preserved and the RPE showed extensive reactionary proliferation. The globe removed 13 months after the insertion of the implant showed total resorption of the polymer; the site of implantation was recognised by thinning of the sclera, which contained clusters of foamy macrophages. Here there was fusion between a gliotic retina and a thin band of fibrotic choroid with an interposed layer of atrophic RPE.

Apart from the area of the inlay all the other ocular structures in all experimental eyes showed no significant differences from the appearance of the control tissue.

Discussion

Suprachoroidal insertion of a small portion of dehydrated hydrophilic polymer is followed by hydration of the polymer in situ and the production of an elevation of the overlying choroid and retina. The depth of the indent is determined by the size of the initial implant but is approximately 10 times the volume of the dehydrated insert.

A suprachoroidal plombe of hydrophilic polymer is well tolerated in the rabbit eye and has caused no clinically unacceptable complications in a series of rabbits over periods of time up to one year. Nevertheless, the histological reactions are of interest. The most striking effect is the mononuclear macrophagic

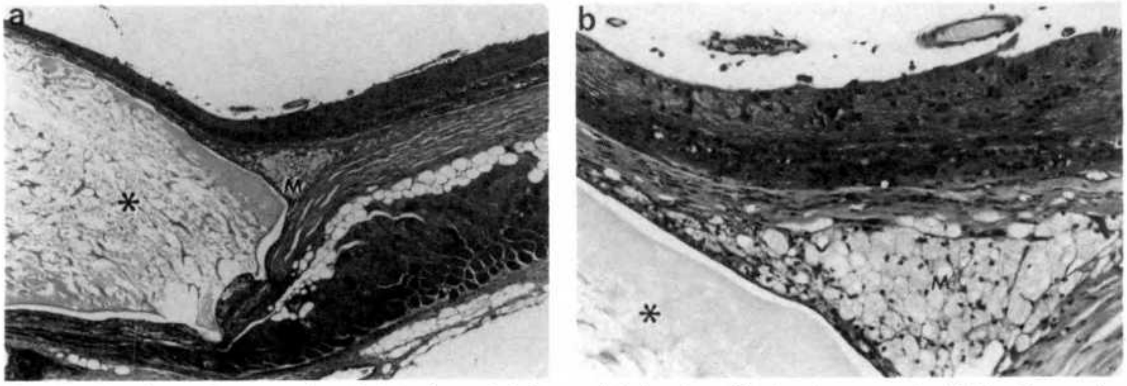


Fig. 10 *Histology of a suprachoroidal implant of 4–5 months' duration. The implant space is filled with granular eosinophilic material* (*) *and surrounded by foamy macrophages* (M). *The choroid is fibrotic and fused to the overlying RPE and retina.* (a) ×*26.* (b) ×*110.*

response to the polymer and the adjacent fibrosis in the choroid. The latter appears to be variable in extent. In some specimens choroidal fibrosis lead to total retinal atrophy, while in others there was preservation of the inner retina and reactionary proliferation of the RPE. The net effect in each specimen was that there was a broad zone of chorioretinal fusion similar to that resulting from therapeutically applied cryotherapy.

The use of this material as a suprachoroidal plombe in the management of human retinal detachment may be justified. A urethane based polymer in the form of a sponge has been successfully used as an episcleral indent,[2] and another hydrophilic material has been used successfully as an episcleral or intrascleral inlay.[3 4] In neither case has the material been used in the dehydrated state. The use of dehydrated polymer gives the advantage of a slowly enlarging buckle as hydration proceeds and consequent avoidance of raised intraocular pressure and embarrassment of the intraocular circulation which may occur when large changes in intraocular volume are suddenly produced by, for example, episcleral plombage with conventional techniques.

The authors thank Messrs Smith and Nephew for making the hydrophilic polymer available and Mrs Jennifer Murray for typing the manuscript.

References

1 Smith RJ. Suprachoroidal air injection for detached retina. *Br J Ophthalmol* 1952; 36: 385–8.
2 Kothe HW, Lommatzsch PK. Klinische Erfahrungen mit Polyurethan—Weichschaumplomben fur die Netzhautchirurgie. *Klin Monatsbl Augenheilkd* 1985; 187: 273–5.
3 Tolentino FI, Refojo MF, Schepans CI. A hydrophilic acrylate implant for scleral buckling, technique and clinical experience. *Retina* 1981; 1: 281–6.
4 Tolentino FI, Roldan M, Nassif J, Refojo MF. Hydrogel implant for scleral buckling. Long-term observations. *Retina* 1985; 5: 38–41.

Accepted for publication 20 February 1987.

British Journal of Ophthalmology, 1988, **72**, 284–285

A new surgical head rest

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From the Institute of Ophthalmology and Moorfields Eye Hospital, London

SUMMARY A surgical head rest is described that gives good wrist support, provides space to place instruments, and allows drainage of irrigation fluid.

Modern ophthalmic surgical technique demands a high level of micromanipulative skill. The operating microscope permits this precise surgery, and the parallel development of microsurgical instruments, sutures, and techniques makes increasing demand on the manual dexterity of the surgeon. For example, in extracapsular cataract surgery the posterior capsule is only about 6 μm in thickness.

Unfortunately involuntary muscle tremor is always present even in a relaxed surgeon, and increased tremor tends to occur at the most technically demanding parts of the operation, especially if problems occur when there may be raised sympathetic tone in the surgeon.

There are two ways to overcome the limitation of human manual skills. Firstly, technically advanced instruments may provide a mechanical way of performing difficult manoeuvres. For example, the electrically operated scissors used in vitrectomies allow the operator to concentrate on what to cut and free him from making hand movements that merely perform the cutting action. The second way involves providing optimal arm support to the surgeon, and it is the support to the forearm and wrist that is most crucial, providing a steady base for fine finger control of the surgical instruments. Currently used head rests do not always succeed in providing support both to the patient and to the surgeon. The Reuben pillow is widely used and gives good support for the patient's head but no support for the surgeon's wrists. The Lamtec head rest is attached to the end of the operating table, and a variable height pad can be clamped to allow for optimal head position. Independently adjustable rests are then arranged to prevent lateral movement of the head and also provide wrist support precisely where needed. Unfortunately this head rest is cumbersome to use, requiring skilled adjustment for each patient. If the head rest clamp is not tight, there is a danger of sudden extension of the patient's neck. In addition this rest provides no place to leave instruments in frequent use.

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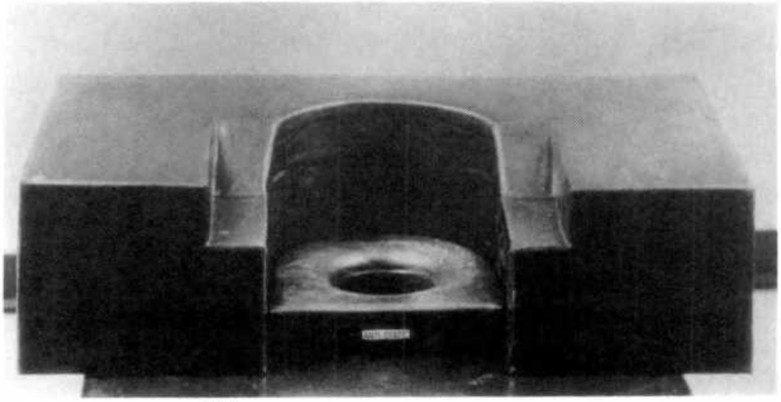

Fig. 1 *The head rest is in two parts so the height of the patient's head can be adjusted, by using extra rings, to suit the position of the surgeon's hands.*

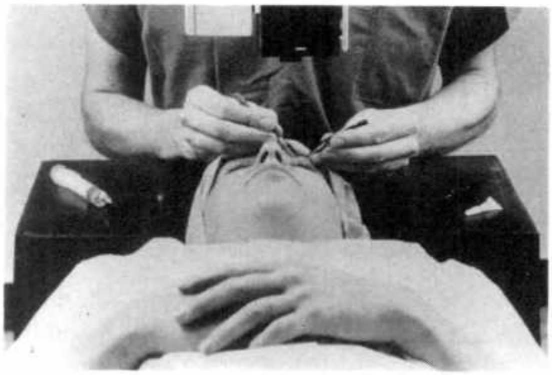

Fig. 2 *The head rest in use showing the wide area for instruments and the drainage channels either side of the patient's head where a towel may be placed to mop up irrigating fluid.*

The head rest

The head rest described here was developed to maximise wrist support for the surgeon at an appropriate position in relation to the patient's eye. A wide wrist rest is needed so that at different stages of the operation—for example, suturing each end of a cataract section—the support falls naturally to hand. It is desirable to be able to adjust the height of the support in relation to the position of the patient's eye. It is also helpful to have a place to put surgical instruments for both the assistant and the surgeon and also to make some arrangement for the volumes of extracapsular irrigating fluid that uncollected could form large pools.

Fig. 1 shows the final design of the head rest and Fig. 2 shows it in use with a 'patient' and a 'surgeon'. It consists of two parts, a ring for the patient's head to rest on, and the main body of the pillow, which is constructed with a solid base and a very firm foam upper part covered with standard waterproof antistatic material. The pillow is as wide as the operating table and the whole of this width is available for wrist support. Using extra rings for the patient's head as required enables the height of the head and thus of the eye in relation to the surgeon's wrist to be adjusted; this adjustment is made with the help of the anaesthetist. For patients with neck problems, in whom flexion and extension are limited, the anaesthetist may adjust the number of rings used to suit him rather than the surgeon. Flat areas either side of the head are suitable for placing instruments in frequent use, and cut-outs directly adjacent to each eye allow space for a rolled up towel to absorb irrigation fluid. The area for instruments may also be used as a wrist rest when the surgeon's arm is round the side of the eye, as when placing difficult sutures in graft surgery.

In practice most surgeons who have tried this head rest find that it is almost immediately comfortable, providing support in an unobtrusive way. It also appears to be comfortable for patients under a local anaesthetic. The lack of moving parts such as are found in some other head rests make it popular with theatre staff, as it is quick and easy to set up for each patient.

This head rest is available from Dixey Instruments Ltd, 19 Wigmore Street, London W1A 4DU. The author has no connection with Dixey Instruments and has no financial interest in this head rest.

Accepted for publication 26 February 1987.

British Journal of Ophthalmology, 1988, 72, 286–288

Radiotherapy in benign orbital disease. I: Complicated ocular angiomas

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SUMMARY Radiotherapy has been successful in the management of complicated ocular and orbital angiomas, but late morbidity (particularly radiation induced cataract) has been a problem. With modern radiotherapy techniques it is possible to minimise the morbidity to other tissues. By means of a recently developed method of lens-sparing ocular radiotherapy (initially adopted for retinoblastoma therapy) two cases of diffuse ocular haemangioma complicated by retinal detachment have been treated, with evidence of regression.

It has been well established that the majority of haemangiomas of childhood are harmless and require no treatment and that the majority of capillary haemangiomas will spontaneously regress.[1 2] Although radiotherapy has historically been used to induce regression of paediatric haemangiomas,[1 3] this treatment is now considered to be contraindicated in most cases. Furthermore, steroid therapy has been shown to induce regression of such haemangiomas,[4] including orbital haemangiomas,[5-8] and when therapy is indicated this form of treatment is preferred to radiation therapy, though its success rate has not been high in all workers' experiences.[9 10]

The commonest site for orbital haemangiomas in childhood is in the anterior orbit and upper lid.[10] In the large New York series the high incidence of tumour-associated, late visual sequelae (namely, amblyopia, anisometria, strabismus, optic nerve atrophy) prompted the authors to advise early treatment with both steroids and radiotherapy for large lesions, though the data from treated cases still reflected a high incidence of tumour-associated sequelae.[10]

The radiotherapeutic management of lid haemangiomas is relatively straightforward, as a lead eye shield, placed behind the lids and against the eye, protects the eye itself from the superficial *x*-rays which are used to treat the lid. This is an established technique that requires little further comment.

However, a number of complicated ocular angiomas remain (both haemangiomas and lymphangiomas), situated behind the lids, around the globe, within the eye itself, or posteriorly within the orbit, for which there has correctly been great concern for late morbidity associated with radiotherapy. Two such cases presenting recently to the joint ocular oncology unit of St Bartholomew's and Moorfields hospitals are presented here to illustrate a method of treatment designed to minimise morbidity associated with the treatment.

Case reports

CASE 1

This 12-year-old girl was born with a 'port wine' stain over her right upper lid associated with vascular conjunctival and episcleral injection of that eye. However, the child's eyesight had been checked by an optician at age 7 and was said to have been good in both eyes. The child presented to an ophthalmologist at 11 years because of decreased vision in the right eye. On examination there was an upper right facial port wine stain involving the upper lid, with markedly dilated episcleral and conjunctival vessels. The right corneal diameter was greater than the left. The intraocular pressure was raised in the right eye. Retinoscopy showed +7 dioptres of hypermetropia in the right eye, and on funduscopy showed a serous detachment of the posterior retina including the macula and pericapillary area, with a probable underlying haemangioma. The left fundus was normal. Visual acuity was reduced to counting fingers on the right.

The diagnosis was that of a variant of the Sturge-

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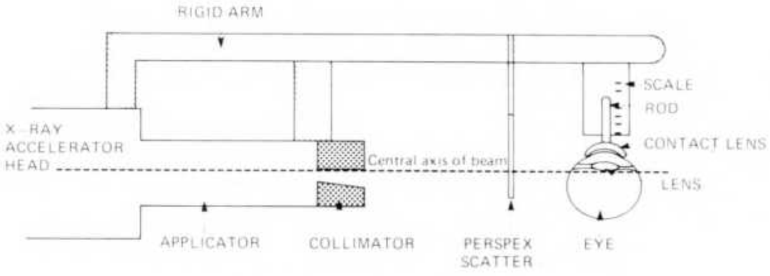

Fig. 1A *Schematic drawing of lens-sparing ocular radiotherapy technique. The non-divergent, penumbra-trimmed anterior beam edge is positioned at the back of the lens (Harnett* et al.[12]*).*

Weber syndrome, including a choroidal haemangioma and serous retinal detachment.

Treatment began with external beam radiotherapy. The technique used was that developed for retinoblastoma therapy—that is, a penumbra-free, non-divergent anterior beam edge from a linear accelerator source was positioned with high accuracy, via a contact lens reference point on the cornea, behind the lens of the eye to provide a lens-sparing ocular portal (Figs. 1A, B). A tumour dose of 1200 cGy was delivered in eight fractions over nine days (6 MV photons).

Nine months later the retina was flat, the haemangioma smaller, and the intraocular pressure reduced, but the visual acuity remained at counting fingers. The fluorescein angiograms demonstrate the improvement before and after radiotherapy (Figs. 2A, B).

CASE 2

This girl was initially examined ophthalmologically at the age of 1 year, when she had a vascular lesion on the right cheek. She was then noted to have abnormal pigmentation of the iris inferiorly and extensive pigmentation in the right fundus inferiorly and temporally. There was no evidence of any angiomatous lesion in the fundus. At age 4 years a considerable number of enlarged vessels were noted in the iris, and the fundus had angiomatous vessels and an area of pigmentation and choroidal atrophy. Visual acuities were 6/24 right eye, 6/4 left eye. The visual acuity in the right eye had deteriorated to 6/60 at the child's presentation to this centre at age 6½ years, and at this time there was an obvious and very large choroidal haemangioma in the inferior mid-periphery with associated serous retinal detachment. By ultrasound examination the haemangioma was found to have a base diameter of 17 mm and it was 6 mm thick.

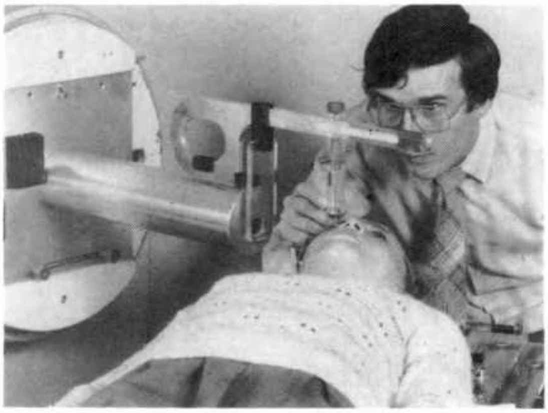

Fig. 1B *Patient (case 1) being positioned for a treatment.*

By means of the lens-sparing external beam, ocular radiotherapy technique (as for case 1) a tumour dose of 1200 cGy was delivered in eight fractions over 12 days (6 MV *x*-rays). Six months later the retina was flat and the tumour was smaller. The visual acuity had improved to 6/36.

Discussion

Although radiotherapy has been used to treat orbital angiomas for many years, the indications for such treatment have in recent years been confined to large and complicated cases. While discrete haemangiomas causing retinal detachment have previously been treated by laser photocoagulation or cobalt plaque therapy, the diffuse ocular haemangiomas presented in the two cases here could not be so treated.

When modern radiotherapeutic techniques are used, their sophistication allows treatment to occur with only a small risk of late treatment-related morbidity. This last fact bears directly on the timing of future recommendations for radiotherapy, particularly when the incidence of the late visual complications of angioma is high.[10] Early radiotherapy for intraocular angiomas would not previously have been contemplated by ophthalmologists mindful of the literature on morbidity related to treatment.[11]

In the cases reported here a modern method of lens-sparing ocular radiotherapy, developed for retinoblastoma therapy,[12] was employed to treat ocular haemangiomas complicated by serous retinal detachments and visual deterioration. In both cases

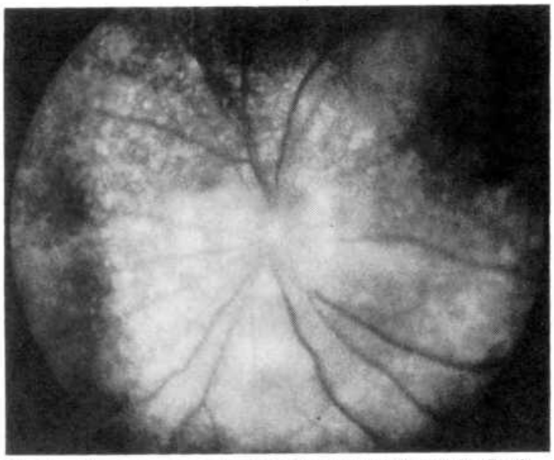

Fig. 2 *Fluorescein angiogram photographs (case 1). Both figs. 2A and 2B represent the recirculation phase at 10 minutes after injection. Fig. 2A was taken prior to radiotherapy and shows slow clearing of the dye.*

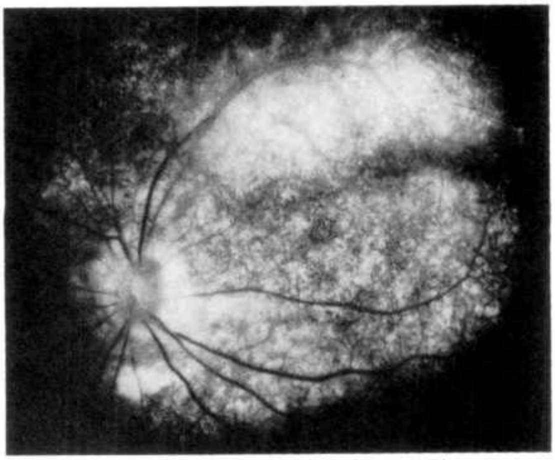

Fig. 2B *Taken six months after radiotherapy. There is more rapid clearing of the dye; the retina has flattened and become reattached.*

the therapy was effective in causing regression of the angioma and reversal of the retinal detachment; return of vision was limited by the pretreatment extent of the retinal detachment. Our retinoblastoma practice has established the safety and accuracy of this external beam radiotherapy technique, which was adapted for use under local anaesthesia to the eye in the two cases reported here. Having established the safety and efficacy of this treatment, we would now recommend the earlier treatment of patients such as these in the expectation that visual deterioration would be arrested at an earlier stage.

In conclusion, radiotherapy remains an important form of treatment for orbital angiomas, and with the lesser morbidity of modern methods earlier treatment than previously may be indicated. Although radiotherapy for any benign lesion requires careful individual consideration, this treatment method remains appropriate, important, and effective therapy for some patients.

It is with great pleasure that we thank Mr J Hungerford and Mr D Taylor for referring patients and Miss T Cocks for typing the manuscript.

References

1 Walter J. On the treatment of cavernous haemangioma with special reference to spontaneous regression. *J Fac Radiol* 1953; **5:** 134–40.

2 Bowers RE, Graham EA, Tomlinson KM. The natural history of the strawberry nevus. *Arch Dermatol* 1960; **82:** 667–80.

3 Martin LW, MacCollum DW. Hemangiomas in infants and children. *Am J Surg* 1961; **101:** 571–80.

4 Zarem HA, Edgerton MT. Induced resolution of cavernous hemangiomas following prednisolone therapy. *Plast Reconstr Surg* 1967; **39:** 76–83.

5 de Venecia G, Lobeck CC. Successful treatment of eyelid hemangioma with prednisone. *Arch Ophthalmol* 1970; **84:** 98–102.

6 Hiles DA, Pilchard WA. Corticosteroid control of neonatal hemangiomas of the orbit and ocular adnexa. *Am J Ophthalmol* 1971; **71:** 1003–8.

7 Kushner BJ. Local steroid therapy in adnexal hemangioma. *Ann Ophthalmol* 1979; **11:** 1005–9.

8 Zak TA, Morin JD. Early local steroid therapy of infantile eyelid hemangiomas. *J Pediatr Ophthalmol Strabismus* 1981; **18:** 25–7.

9 Henderson JS. *Orbital tumours*. Philadelphia: Saunders, 1973: 124–67.

10 Haik BG, Jakobiec FA, Ellsworth RM, Jones IS. Capillary hemangioma of the lids and orbit: an analysis of the clinical features and therapeutic results in 101 cases. *Trans Am Acad Ophthalmol* 1979; **86:** 760–89.

11 Bek V, Zahn K. Cataract as a late sequel of contact roentgen therapy of angiomas in children. *Acta Radiol (Stockh)* 1960; **54:** 443–8.

12 Harnett AN, Hungerford J, Lambert GD, *et al.* Improved external beam radiotherapy for the treatment of retinoblastoma. *Br J Radiol* 1987; **60:** 753–60.

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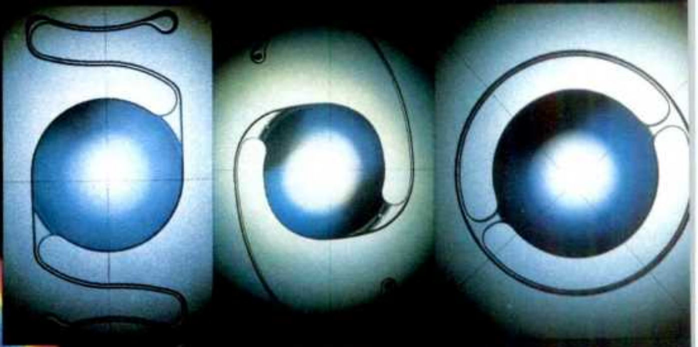

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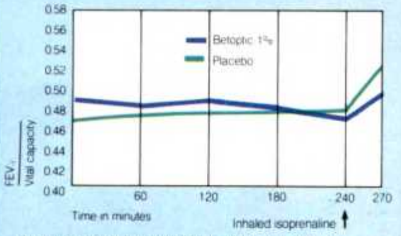

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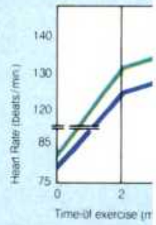

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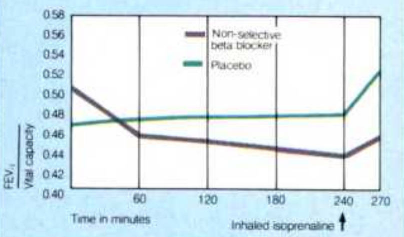

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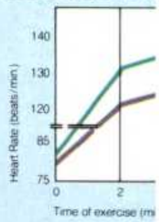

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FERENCES: 1. Schoene, R B et al., Am J Ophthalmol, 97:86-92, 1984. **2.** Atkins, J M., et al., Am J. Ophthalmol, 99:173-175, 1985. **3.** Cervantes, R., et al., J. Toxicol-Cut and Ocular Toxicol., 5 -193. 1986 . **4.** Dunn T.L. et al., Am. Rev. Respir. Dis., 1331:264-268 1986. **5.** Data on file at Alcon Research and Development.

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British Journal of Ophthalmology, 1988, 72, 289–292

Radiotherapy in benign orbital disease. II: Ophthalmic Graves' disease and orbital histiocytosis X

A N HARNETT, D DOUGHTY, A HIRST, AND P N PLOWMAN

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SUMMARY Ophthalmic Graves' disease and histiocytosis X involving the orbit are occasionally refractory to treatment, so that vision may be threatened. In these situations megavoltage external beam radiotherapy should be employed, and the indications for this treatment are discussed. A highly accurate technique is described, using precise planning with information obtained from high definition CT scans, a complete patient head shell for immobilisation, and modern megavoltage radiotherapy treatment machines. As a result the dose to the lens is minimised (to a maximum of 10% of the prescribed dose), and late morbidity will be small. Two cases are described to illustrate this procedure and the response to treatment.

It is accepted practice that radiotherapy should be confined to the treatment of malignant disorders apart from exceptional circumstances. There exist benign orbital disorders which prove refractory to other treatments and, when imminently threatening vision, are well treated by low-dose external beam radiotherapy to the orbits. In such cases the radiotherapist is under a strict obligation to minimise any possible late tissue morbidity.

Orbital Graves' disease is a poorly understood condition that responds to low-dose orbital radiotherapy. The orbit and extraocular muscles are infiltrated by inflammatory cells, notably lymphocytes, and it is the exquisite sensitivity of the lymphocyte to steroids and radiation that is the rationale for this immunosuppressive treatment. The initial studies employed radiotherapy directed at the pituitary orbital regions using conventional orthovoltage equipment.[1 2] The poorly collimated orthovoltage beams, with their considerable penumbra together with crude treatment planning, led to effectively large treatment portals being used. With modern radiotherapy for ophthalmic Graves' disease it is the tight collimation of the beam and the extreme accuracy of beam position that minimise late morbidity. Megavoltage radiotherapy was first employed for ophthalmic Graves' disease in 1973,[3] and it is this Stanford technique that has laid the foundations of the modern techniques, one development of which is described here.

Another aetiologically obscure condition is histiocytosis X, which is no longer considered to be a malignant tumour.[4 5] The bones of the skull are a site of predilection, and occasional cases of complicated orbital disease occur. A considerable body of literature has now recorded the efficacy of low-dose radiotherapy in such cases.[5-7] Orbital radiotherapy is indicated where steroids have proved unsuccessful in arresting progressive orbital histiocytosis X and probably before administering systemic mutagenic chemotherapy for a local problem.

We here describe the technique used at St Bartholomew's Hospital to treat patients with orbital Graves' disease and histiocytosis X refractory to other forms of therapy and illustrate the technique with clinical examples of both conditions.

Material and methods

TECHNIQUE

Orbital radiotherapy is applied with a similar technique for both ophthalmic Graves' disease and histiocytosis X.

A high-definition computer tomography (CT) scan of the orbits is obtained before planning the radiotherapy. Cursor measurements from the lids to the

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back of the lens and the back of the globe aid planning. Standard tables of ocular dimensions supplement these data.[8]

A supine plastic immobilisation head shell is made for each patient. This two-part device provides rigid confinement of the patient's head throughout the therapy session. Bilateral opposed temporal beam portals are planned on the treatment simulator. The superior and inferior field borders are defined by the orbital bony margins, and the posterior volume is set at the back of the orbital cone. The anterior field border is ascertained retrospectively by the planning constraint that the 10% isodose must be the maximum dose received at the back of the lens. A transverse section of the patient's head is taken at the level of the canthi with the lids closed; the positions of the orbits are marked in accord with CT data. Dose distribution (isodose) from the radiation portals is superimposed on this section, see Figs. 2 and 4. The lateral 6 MV photon beams are angled posteriorly by their divergent angle so that the anterior field borders are parallel to the back of both lenses. In addition, to aid dose homogeneity, the fields are 'wedged', accommodating the change in patient contour anteriorly.

It is recognised that in order to spare the lens anteriorly sited swellings (notably the oedematous upper lid so common in ophthalmic Graves' disease) will not be encompassed within the primary beam. In Graves' disease placement of the posterior field border is influenced further by the requirement to retain pituitary dose level below 50% of the prescribed dose. Routine thermoluminescent dosimeters are employed on the lids of both eyes to check the dose is minimal in these regions.

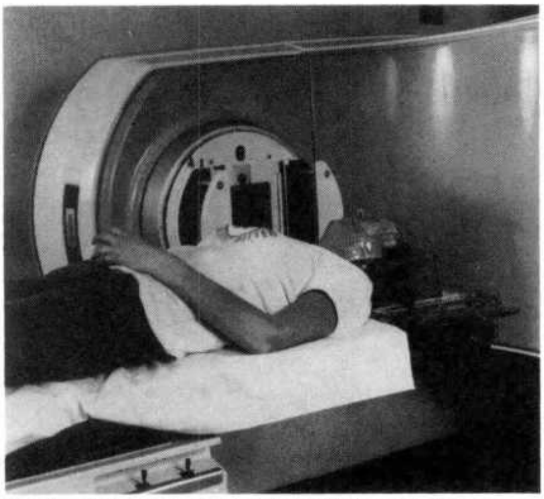

Fig. 1 *Patient (case 1) set up for radiotherapy. Note immobilisation head shell and treatment planning marks.*

CASE REPORTS

Case 1

This 32-year-old district nurse developed thyrotoxicosis three years earlier which was poorly controlled on carbimazole but responded well to partial thyroidectomy. For nine months she had developed diplopia with painful and 'bulging' eyes; this last complaint had become very much worse in the months leading up to her presentation. High-dose systemic steroids failed to control the condition. Surgical orbital decompressions brought temporary improvement, but the symptoms returned after three months. The patient was accepted for radiotherapy. At the time of therapy severe diplopia, proptosis, exposure keratitis, and impaired visual acuity (6/36 left eye and 6/24 right) were present.

By the 6 MV x-ray technique described above, a prescribed dose of 2000 cGy was delivered in 12 fractions over 15 days (Figs. 1 and 2), with 100 cGy being given through the lateral portals on the first day. The maximum dose to the lens was 200 cGy.

Visual acuities, which were monitored twice weekly, improved during radiotherapy. The patient's eyes became more comfortable and the diplopia improved. This was maintained and in fact continued at one year after treatment, with visual acuities of 6/9 left and 6/6 right.

Case 2

This 2-year-old girl presented with a history of an alternating convergent squint for one year and latterly a swelling over the left zygoma. As the swelling increased in size, the left eye became proptosed. There was a history of 'cradle cap' in infancy and discharging ears, the left worse than the right. From a biopsy from the scalp skin a diagnosis of histiocytosis X was made. Skull x-rays showed two well defined lytic lesions in the left parietal and frontal bones. Also on the plain radiograph there was widening and erosion of the floor of the pituitary fossa, with erosion of the floor of the anterior cranial fossa and of the left sphenoid wing and lateral wall of the orbit extending backwards. CT scanning showed the bony destruction as described, with increased soft tissue disease at the back of the left apex and extending across the midline behind both orbits. Visual acuity and the visual evoked responses were normal. The child developed diabetes insipidus, necessitating desmopressin acetate therapy. There was no response to systemic prednisolone.

There was concern that both optic nerves were at risk from the soft tissue retro-orbital disease and the larger bulk of destructive disease in the left orbit.

By the 6 MV x-ray technique described a prescribed dose of 1200 cGy in seven fractions over eight days was delivered to the retro-ocular, orbital

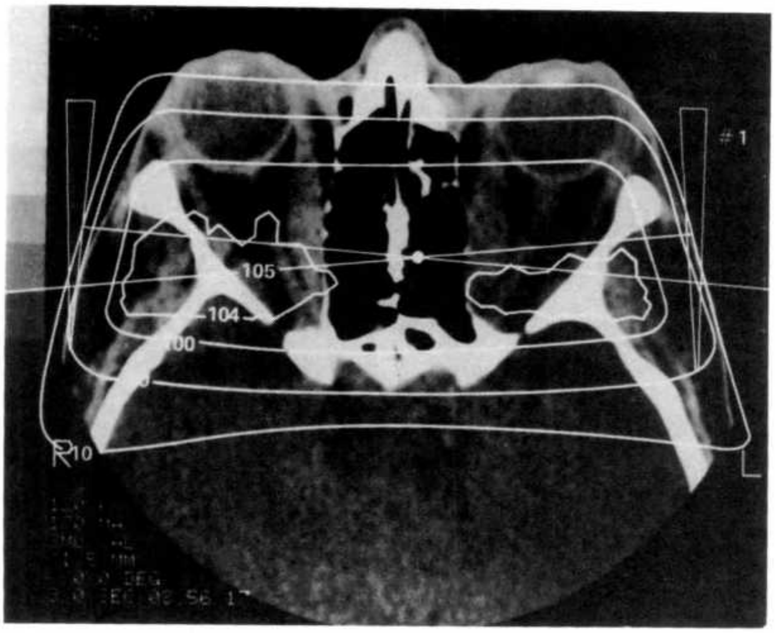

Fig. 2 *CT scan of the orbits (case 1). Radiation isodoses are superimposed showing 10% isodose at back of lens and 100% encompassing the back of the orbital cone. Note also the greatly enlarged medial rectus muscles.*

regions, the treatment volume extending further posteriorly than in case 1 to encompass the retro-orbital soft tissue extension, hypothalamus, and pituitary (Figs. 3 and 4). However, a lower dose was employed.

The diabetes insipidus did not respond. The swelling in the left zygoma region and the proptosis regressed over a few months and remained so at one year. Magnetic resonance imaging at nine months after therapy confirmed less soft tissue disease. The child remains well.

Discussion

Traditional reluctance to employ radiotherapy for benign orbital disease has been based on anxiety concerning late morbidity, notably cataractogenesis. However, with modern radiotherapeutic techniques, well collimated x-ray beams can treat the orbit while keeping the lens below its cataract threshold. The technique described here relies on modern treatment equipment and on known depths of critical ocular points by high definition CT scanning with cursor measurements, supplemented by standard tables of ocular measurements. In addition, and critically, a head fixed by a full head shell allows reproducibility of positioning. These factors allow the dosimetric advance over previous treatment methods which historically used orthovoltage x-rays or telecobalt beams, the lateral skin canthus as the set-up mark for the anterior field edge or a bite block only to support the head.

In 1951 Jones[9] described a series of 29 patients with Graves' ophthalmopathy treated by radiotherapy at St Bartholomew's Hospital. He showed that it is the patients with fast, progressive, and serious disease that respond best to radiotherapy, an observation that has been confirmed by others.[3] Glaser[10] considered that the indications for orbital radiotherapy in Graves' ophthalmopathy were only two: these are steroid refractory patients with 'documented optic neuropathy with visual acuity less than 20/40 or an acute painful inflammatory phase of Graves' disease'. Our own indications also include pro-

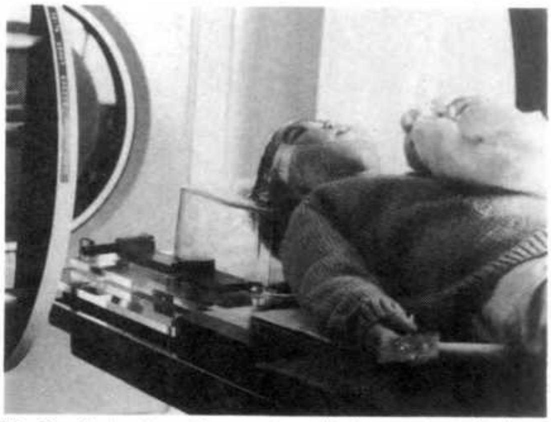

Fig. 3 *Patient (case 2) set up for radiotherapy for orbital histiocytosis X. The immobilisation head shell is again important for precision treatment.*

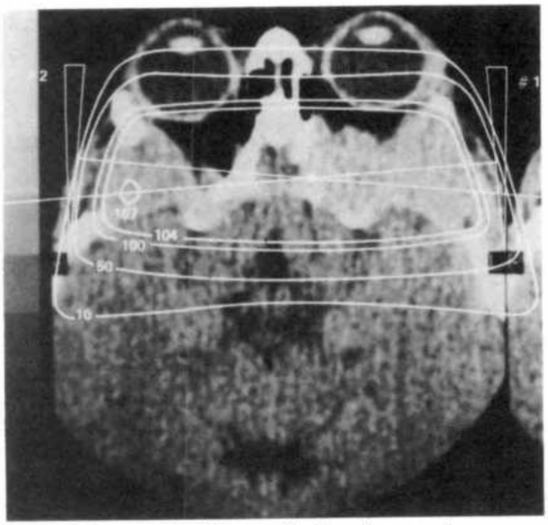

Fig. 4 *CT scan of orbits (case 2). Note the extensive involvement of the posterior orbital tissues by histiocytosis X is easily seen. Planning has been performed so that the 100% isodose includes the posterior aspect.*

gressive diplopia or progressive exposure keratitis following failure of steroid therapy, but we agree with Glaser's general conclusion that the technique is not indicated for uncomplicated disease.

Similarly, the indications for radiotherapy in orbital histiocytosis X must be strict, but, as in the child reported on here, imminent visual compromise remains an important indication.

In conclusion, there remain complicated cases of benign orbital disease for which radiotherapy is indicated and in which, with techniques such as those described here, late morbidity will be small and the benefit to the patient immense.

It is with great pleasure that we thank Mr P Fells, Dr B Shine (Moorfields Hospital), Professor G M Besser (St Bartholomew's Hospital), and Dr J Pritchard (Hospital for Sick Children, London) for referring patients. Miss T Cocks kindly typed the manuscript.

References

1 Ginsburg S. Postoperative progressive exophthalmos, with low basal metabolic rate. *Ann Intern Med* 1939; **13:** 424–50.
2 Mandeville FB. Roentgen therapy of orbital-pituitary portals for progressive exophthalmos following subtotal thyroidectomy. *Radiology* 1943; **41:** 268–71.
3 Donaldson SS, Bagshaw MA, Kriss JP. Supervoltage orbital radiotherapy for Graves' ophthalmopathy. *J Clin Endocrinol Metab* 1973; **37:** 276–85.
4 Osband ME, Lipton JM, Laving P, *et al.* Histiocytosis X. Demonstration of abnormal immunity. T cell histamine H2-receptor deficiency and successful treatment with thymic extract. *N Engl J Med* 1981; **304:** 146–53.
5 Nesbit ME. Current concepts and treatment of histiocytosis X (Langerhans' cell histiocytosis). In: Voute PA, Barrett A, Bloom HJG, Lemerle J, Neidhardt MK, eds. *Cancer in children*. Berlin: Springer, 1986: 176–84.
6 Childs DS, Kennedy RLJ. Reticuloendotheliosis of children: treatment with roentgen rays. *Radiology* 1951; **57:** 653–9.
7 Ochsner SF. Eosinophilic granuloma of bone; experience with 20 cases. *AJR* 1966; **97:** 719–26.
8 François J. Ocular biometry. *Doc Ophthalmol Proc* 1981; **29:** 135–64.
9 Jones AE. Orbital *x*-ray therapy of progressive exophthalmos. *Br J Radiol* 1951; **24:** 637–46.
10 Glaser J. Editorial: Graves' ophthalmopathy. *Arch Ophthalmol* 1984; **102:** 1148–9.

Accepted for publication 26 February 1987.

British Journal of Ophthalmology, 1988, 72, 293–298

Active cytomegalovirus particles in the eyes of an AIDS patient being treated with 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (Ganciclovir)

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SUMMARY The eyes of an AIDS patient with cytomegalovirus (CMV) retinitis and pneumonitis who died while receiving maintenance therapy with the antiviral agent 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (Ganciclovir) were obtained for pathological examination. While under treatment the patient had significant improvement but not complete regression of retinitis. Electron microscopic and immunofluorescent techniques revealed cytomegalovirus particles in the retina, sclera, iris, and ciliary body. These findings are consistent with a virostatic type of inhibition of CMV by this agent. They also suggest that CMV involvement in the eye and other organs may be more widespread than is clinically apparent in AIDS patients.

Cytomegalovirus (CMV) infections occur commonly in patients with the acquired immunodeficiency syndrome (AIDS) and represent an important cause of morbidity and mortality in these patients.[1-3] The retina is frequently involved by CMV,[4-7] and retinitis may be the first clinical sign of disseminated infection with this organism.[8] Untreated CMV retinitis in AIDS patients relentlessly progresses to involve the entire retina, resulting in irreversible blindness.[5] Recently a new antiviral agent 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (Ganciclovir) or BWB759U (Burroughs Wellcome Co., Research Triangle Park, North Carolina), has been shown to effect at least stabilisation or partial improvement of CMV retinitis in over 80% of the affected eyes in immunosuppressed patients treated with this drug.[9-12] Unfortunately, the vast majority of these patients with AIDS have relapses within two to six weeks of discontinuing therapy.[9-14] This has led some investigators to believe that long-term intravenous therapy will probably be necessary.[9-14] We report here the clinical course and histopathological and ultrastructural findings in the eyes of an AIDS patient with CMV retinitis and pneumonitis who died while receiving maintenance intravenous therapy with Ganciclovir.

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Case report

A 30-year-old homosexual white male was admitted to Beth Israel Medical Center 4 September 1985 for an episode of dysphasia and dizziness lasting 4–5 hours. AIDS had been diagnosed in November 1984 when he developed *Pneumocystis carinii* pneumonia. For three months prior to admission he had persistent diarrhoea due to biopsy-proved cytomegalovirus (CMV) colitis. He had also developed generalised weakness of his arms and legs for six weeks before admission due to an AIDS-related peripheral neuropathy.

On admission the patient had no visual complaints, but an ophthalmic consultation was requested because of a cotton-wool spot noted in the left eye. An ophthalmic examination of 6 September 1985 revealed a best corrected vision of 20/25 in each eye. Ocular motility, confrontation visual fields, and pupillary reactions were normal, with no afferent pupillary defect. Slit-lamp examination showed normal anterior segments except for dilated segments of conjunctival venules near the nasal limbus OU. Ophthalmoscopic examinations, with dilated pupils, of the fundi with direct and indirect ophthalmoscopy showed an area of yellowish perivascular opacification in the far inferotemporal retina of the right eye without evidence of vitreous inflammation. This area was 2·5 disc diameters in size and was consistent clinically with CMV retinitis. A cotton-wool spot was present along the inferotemporal arcade of the left eye. No other fundus abnormalities were noted.

A serum CMV enzyme-linked immunosorbent assay (ELISA) was equal to 0·67. A toxoplasmosis titre was negative. Serum and urine cultures for CMV were negative. A lumbar puncture did not reveal any cells or organisms in the cerebrospinal fluid (CSF), and all cultures including viral cultures of the CSF were negative.

The patient was discharged after five days without determination of a cause for his acute neurological symptoms, which did not recur.

He was readmitted 10 October 1985 because of progressing limb weakness, fever to 39·4°C, and diffuse interstitial pulmonary infiltrates on his chest *x*-ray. He still appeared to be asymptomatic. An ophthalmic examination on 15 October 1985 showed the best corrected visual acuity to be 20/25 OU. Ophthalmoscopy of the right eye showed the retinitis to have progressed along the inferotemporal vessels to within 2 disc diameters of the inferotemporal arcade. No retinitis was seen in the left eye. An endobronchial biopsy on 17 October 1985 revealed *Pneumocystis carinii* organisms, and culture of the biopsy material subsequently grew cytomegalovirus. Because it was thought that visual loss in the right eye was imminent, the patient was given intravenous pentamidine, and treatment with Ganciclovir (supplied by the Burroughs Wellcome Co. on a compassionate plea protocol) was begun on 17 October 1985 at a dosage of 2·5 mg/kg intravenously every eight hours. A white blood cell count (WBC) at this time was $13\cdot2\times10^9$/l and haemoglobin (Hb) was 9·6 g/dl. Over the next 24 hours there was a slight extension of the retinitis in the right eye, which then stabilised. By the 13th day of treatment partial fading of the area of retinitis in the right eye was observed, with no change in visual acuity. He was afebrile, with less diarrhoea and improvement of the pulmonary infiltrates on chest *x*-ray. On the 21st day of treatment vision was still 20/25 OU, with marked improvement in the retinitis of the right eye. The initial area of acute retinitis was converted into a granular pigmented chorioretinal scar with a thin surrounding rim of residual retinitis (Fig. 1). The same dosage of Ganciclovir was continued until his discharge from the hospital on 13 November 1985 for a total of 28 days. At this time his vision was unchanged and the residual rim of retinitis in the right eye was fainter. He remained afebrile, his pulmonary infiltrates had cleared, and the WBC was $4\cdot7\times10^9$/l. Serum and urine cultures for CMV were negative.

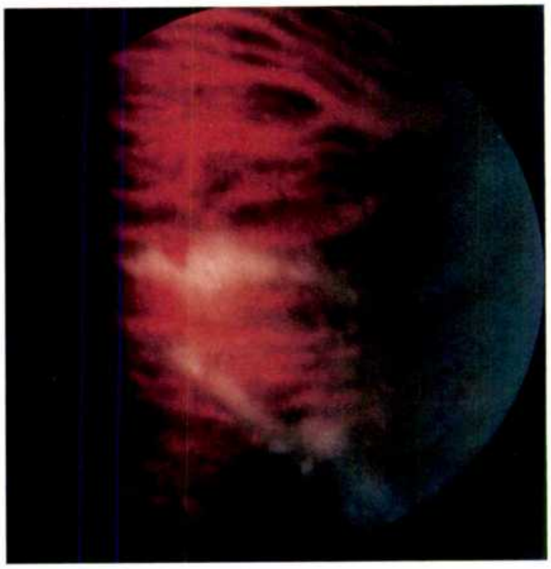

Fig. 1 *Fundus photograph of right eye taken 22 days after beginning therapy with Ganciclovir demonstrating residual CMV retinitis around the edges of chorioretinal scarring just outside the inferotemporal arcade.*

On leaving the hospital the patient was put on a home maintenance programme of Ganciclovir at a dosage of 5 mg/kg intravenously once daily for five days per week.

He was examined again on 21 November 1985, when he had no visual complaints and his vision was still 20/25 OU. The residual retinitis in the right eye was less prominent round the chorioretinal scar, but two spots of retinal opacification each about ⅓ of a disc diameter were seen in the temporal peripheral retina of the left eye, suggestive of early foci of retinitis.

On 5 December 1985 his vision was unchanged, but there was a slight increase in the density and width of the area of retinitis surrounding the chorioretinal scar inferotemporal to the posterior pole of the right eye. There was no change in the left eye. The WBC was now 4×10^9/l. The home dosage of Ganciclovir was increased to 5 mg/kg each morning and 2·5 mg/kg each evening every day. This was continued for 21 days, and on 26 December 1985 his vision was still 20/25 OU, with no change in the retinitis of either eye. The dosage of Ganciclovir was then reduced to 5 mg/kg once a day for seven days a week. His

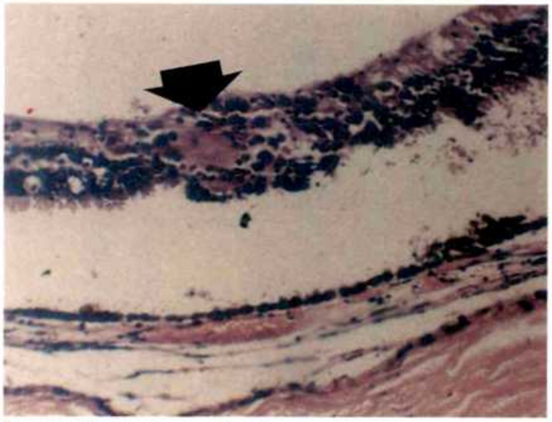

Fig. 2 *Photomicrograph of retina at level of the equator showing an area of retinal necrosis (arrow) and retinal pigment epithelial degeneration. Haematoxylin and eosin. ×216.*

WBC during this time fluctuated between 2·4 and $3{\cdot}0\times10^9$/l.

The patient was again admitted to hospital on 29 December 1985 for bilateral pneumonia with a right sided pleural effusion after 46 days of home maintenance Ganciclovir. His WBC at this time was $5{\cdot}5\times10^9$/l. An ophthalmic examination on 30 December 1985 showed his vision to still be 20/25 OU, with no change in the retinitis of either eye—neither regression nor progression. He was maintained on 5 mg/kg Ganciclovir daily. Blood and pleural fluid cultures grew *Staphylococcus aureus*. All cultures were negative for cytomegalovirus. Despite treatment with appropriate antibiotics the patient died from respiratory arrest on 2 January 1986 after a total of 76 days of treatment with Ganciclovir. Consent was obtained for post-mortem removal of the eyes.

PATHOLOGICAL EXAMINATION

Gross examination of the right eye revealed an intact globe measuring 25×24·5×24·5 mm with 8 mm of attached optic nerve. The globe transilluminated normally and was opened through the plane of retinal involvement that had been described clinically. There were several intraretinal foci of whitish infiltration with associated perivascular cuffing. The optic nerve appeared normal.

Microscopic examination of the right eye revealed a normal anterior segment. The vitreous was clear. Areas of peripheral retina showed perivascular cuffing by neutrophils and rare lymphocytes. An atrophic area of retina was noted just anterior to the equator (Fig. 2). The retinal pigment epithelium here showed a mild disturbance (Fig. 2). There was a prominent area of superficial retinal necrosis which contained cells containing small intracytoplasmic inclusions as well as larger cells with intranuclear 'owl's eye' inclusions (Fig. 3A). Immunoperoxidase stained serial sections demonstrated products specific for cytomegalovirus both in the central necrotic zone and surrounding cells (Fig. 3B). Similarly stained sections specific for CMV revealed virus in the anterior iris stroma (Fig. 4A), surrounding iris vessels, and in the stroma of the ciliary processes (Fig. 4B). Electron micrographs of the retina revealed both typical hexagonally shaped capsomers of herpesvirus (family) and larger more electron-dense forms associated more specifically with cytomegalovirus (Fig. 5).[15]

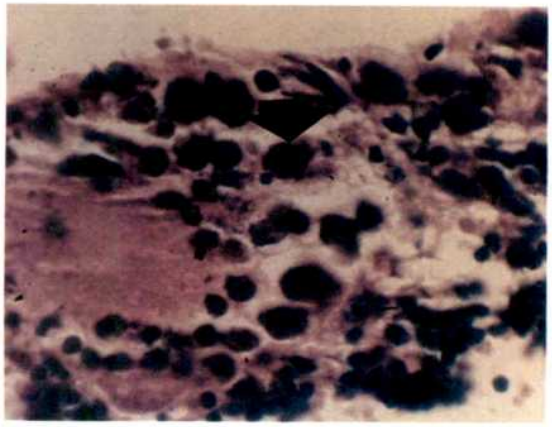

Fig. 3A *Photomicrograph of retina showing a focal area of necrosis. Note cells with viral particles in the cytoplasm (arrow). Haematoxylin and eosin. ×750.*

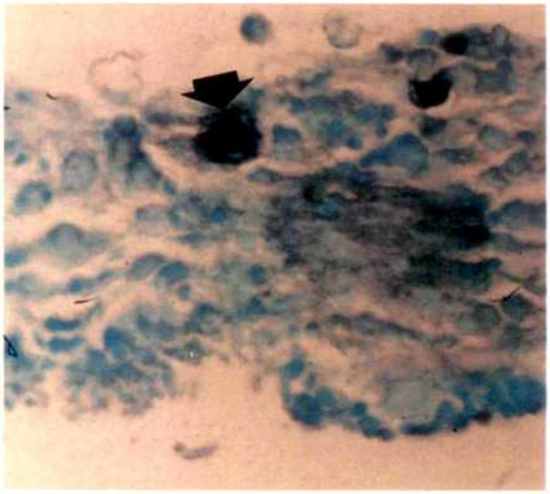

Fig. 3B *Immunoperoxidase stain specific for CMV demonstrates viral material in retina (arrow). ×750.*

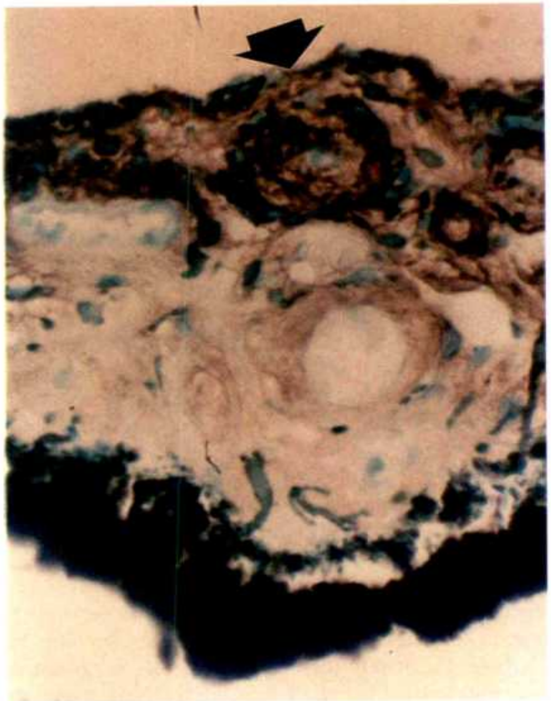

Fig. 4A *Immunoperoxidase stain of iris shows viral material (arrow) in superficial iris (control negative). ×790.*

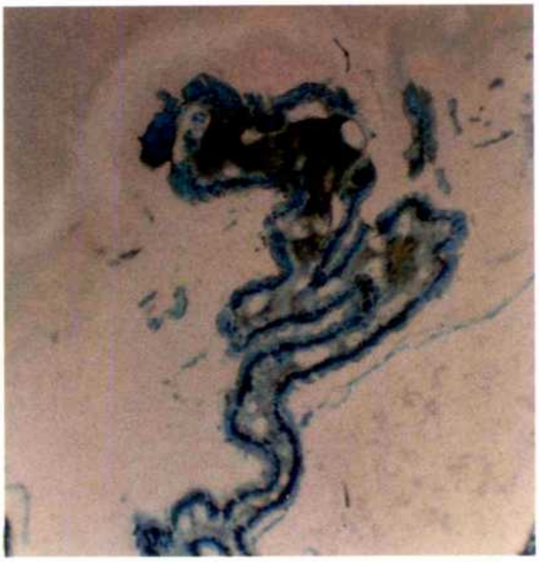

Fig. 4B *Stroma of ciliary processes stain positively with immunoperoxidase (control negative). ×200.*

Discussion

The presence of viral particles suggestive of CMV in the retina of this patient is not surprising, since there was clinically residual retinitis at the time of death. The progression of retinitis, however, was minimal during the time of treatment with Ganciclovir. This is consistent with studies that have demonstrated virostatic reversible-type inhibition of CMV by Ganciclovir.[16 17] The mode of action of Ganciclovir is similar to that of acyclovir in that both are phosphorylated by herpes thymidine kinase and inhibit viral DNA synthesis more than that of the host cell.[18] Ganciclovir is markedly more active than acyclovir against human CMV.[18 19] However, the mechanism of action of Ganciclovir against human CMV has not been fully elucidated. On removal of Ganciclovir, DNA synthesis in CMV resumes and infectious virus reappears.[16 17] Of interest is the demonstration via immunofluorescent techniques of CMV capsular proteins in the sclera, iris, and ciliary body of this patient despite a lack of clinical evidence of disease in these structures. There may not necessarily have been infectious virus in these tissues, since there is greater resistance of viral polypeptide synthesis than of either infectivity or viral DNA synthesis to inhibition by Ganciclovir.[16 17 20] However, CMV has been found on electron microscopic evaluation of the conjunctiva of an AIDS patient who had no clinical evidence of conjunctivitis.[21] This suggests that CMV involvement in the eye and other organs may be more widespread than is clinically apparent in AIDS patients.

Although Ganciclovir was unable to eliminate CMV from the retina and other ocular structures, this patient still appeared to benefit from treatment. He maintained useful vision in both eyes and was relatively visually asymptomatic until his death. He also had clinical improvement in his CMV pneumonitis and colitis.

The virostatic effect of Ganciclovir on CMV shown in this patient and in other studies[9–14] implies that AIDS patients with CMV infections may need to be maintained on this drug indefinitely and that the maintenance dosage should be tailored to the individual. It is conceivable that his CMV retinitis might have regressed further if Ganciclovir had been continued at the higher dosage of 7·5 mg/kg per day. On the other hand drug toxicity, most notably leucopenia,[9–12] may be more common and more severe at higher dosages. This patient did indeed have a lowering of his WBC on the higher dosage. A controlled trial is needed to establish optimum maintenance regimens and to elucidate more fully the efficacy and safety of this drug in AIDS patients. The development of agents not requiring long-term maintenance and of lower toxicity should be sought.

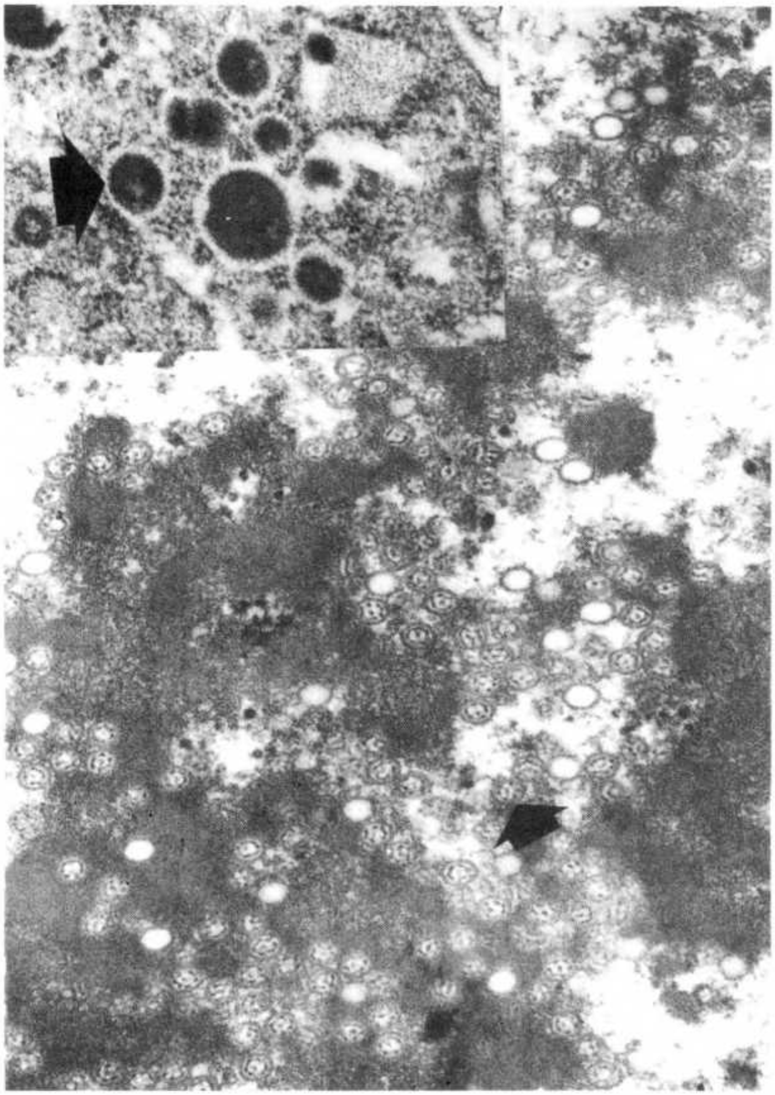

Fig. 5 *Electron micrograph of clinically involved retina reveals hexagonally shaped capsomers of the herpesvirus type. Incomplete forms devoid of capsomers which appear as empty circles. Inset (top left) depicts larger more electron-dense forms consistent with cytomegalovirus within infected cells. ×57 500.*

The 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine was supplied by Donna Cederberg of Burroughs Wellcome Co., Research Triangle Park, North Carolina.

References

1 Quinnan CV, Masur H, Rook AH, *et al.* Herpesvirus infections in the acquired immune deficiency syndrome. *JAMA* 1984; **252:** 72–7.

2 Welch K, Finkbeiner W, Alpers CE, *et al.* Autopsy findings in the acquired immune deficiency syndrome. *JAMA* 1984; **252:** 1152–9.

3 Macher AM, Reichert CM, Straus SE, *et al.* Death in the AIDS patient: role of cytomegalovirus. *N Engl J Med* 1983; **309:** 1454.

4 Holland GN, Pepose JS, Thomas HP, *et al.* Acquired imune deficiency syndrome: ocular manifestations. *Ophthalmology* 1983; **90:** 859–73.

5 Palestine AG, Rodrigues MM, Macher AM, *et al.* Ophthalmic involvement in acquired immunodeficiency syndrome. *Ophthalmology* 1984; **91:** 1092–9.

6 Pepose JS, Holland GN, Nestor MS, *et al.* Acquired immune deficiency syndrome: pathogenic mechanisms of ocular disease. *Ophthalmology* 1985; **92:** 472–84.

7 Reichert CM, O'Leary TJ, Levens DL, Simrell CR, Macher AM. Autopsy pathology in the acquired immune deficiency syndrome. *Am J Pathol* 1983; **112:** 357–82.

8 Murray HW, Knox DL, Green WR, Susel RM. Cytomegalovirus retinitis in adults, a manifestation of disseminated viral infection. *Am J Med* 1977; **63:** 574–84.

9 Palestine AG, Stevens G, Lane HC, *et al.* Treatment of cytomegalovirus retinitis with dihydroxy propoxymethyl guanine. *Am J Ophthalmol* 1986; **101:** 95–101.

10 Masur H, Lane HC, Palestine A, *et al.* Effect of 9-(1,3 dihydroxy-2-propoxymethyl) guanine on serious cytomegalo-

virus disease in eight immunosuppressed homosexual men. *Ann Intern Med* 1986; **104:** 41–4.

11 Collaborative DHPG Treatment Study Group. Treatment of serious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl) guanine in patients with AIDS and other immunodeficiencies. *N Engl J Med* 1986; **314:** 801–5.

12 Rosecan LR, Stahl-Bayliss CM, Kalman CM, Laskin OL. Antiviral therapy for cytomegalovirus retinitis in AIDS with dihydroxy propoxymethyl guanine. *Am J Ophthalmol* 1986; **101:** 405–18.

13 Felsenstein D, D'Amico DJ, Hirsch MS, *et al.* Treatment of cytomegalovirus retinitis with 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine. *Ann Intern Med* 1985; **103:** 377–80.

14 Bach MC, Bagwell SP, Knapp NP, Davis KM, Hedstrom PS. 9-(1,3 dihydroxy-2-propoxymethyl) guanine for cytomegalovirus infections in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1985; **103:** 381–2.

15 Chumbley LC, Robertson DM, Smith TF, Campbell RJ. Adult cytomegalovirus inclusion retino-uveitis. *Am J Ophthalmol* 1975; **80:** 807–16.

16 Mar E-C, Cheng Y-C, Huane E-S. Effect of 9-(1,3 dihydroxy-2-propoxymethyl) guanine on human cytomegalovirus replication in vivo. *Antimicrob Agents Chemother* 1983; **24:** 518–21.

17 Tocci MJ, Livelli TJ, Perry HC, Crumpacker CS, Field AK. Effect of the nucleoside analog 2'-nor-2'deoxyguanosine on human cytomegalovirus replication. *Antimicrob Agents Chemother* 1984; **25:** 247–52.

18 Smee DP, Martin JC, Verheyden JPH, Matthews TR. Anti-herpesvirus activity of the acyclic nucleoside 9-(1,3-dihydroxy-2-propoxymethyl) guanine. *Antimicrob Agents Chemother* 1983; **23:** 676–82.

19 Tyms AS, Davis JM, Jeffries DJ, Meyers JD. BWB759U: an analogue of acyclovir, inhibits human cytomegalovirus *in vitro*. *Lancet* 1984; ii: 924–5.

20 Rasmussen L, Chen PT, Mullenax JG, Merigan TC. Inhibition of human cytomegalovirus replication by 9-(1,3-dihydroxy-2-propoxymethyl) guanine alone and in combination with human interferons. *Antimicrob Agents Chemother* 1984; **26:** 441–5.

21 Teich SA, Tay S, Friedman AH, Schmitterer ME. Viral particles in the conjunctiva of a patient with the acquired immune deficiency syndrome. *Am J Med* 1987; **82:** 151–2.

Accepted for publication 20 February 1987.

NG INFORMATION
hite, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses** Topical ophthalmic
teroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the
nd Administration 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to
age may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.
ons, Warnings, etc. CONTRA-INDICATIONS Acute superficial herpes simplex keratitis. Fungal diseases of ocular
nia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity
nts of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis involving the
great caution. Frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the
cts in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of
r infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or
on has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in
ge group two years or below. This preparation contains benzalkonium chloride and should be used with caution in
hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been
autions As fungal infections of the cornea are particularly prone to develop coincidentally with long-term steroid
gus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra
should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects,
sular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of
side-effects of steroid therapy, ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin.
l Precautions Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper
d 10ml. Basic NHS cost (as at July 1984) 5ml-£1.78, 10ml-£2.83. PL 0426/0028. Full prescribing information is available

FML-NEO* PRESCRIBING INFORMATION
Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, MF0.1% and neomycin sulphate,
BP0.5% (equivalent to 0.35% neomycin base). **Uses** FML-NEO* is indicated for the management of steroid responsive inflammation
the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infection with
neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times daily.
During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to discontin
treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular infections.
Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva and cornea
Ocular tuberculosis. Fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for FML*
above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or activated
the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature indicate a
increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If sensitivi
or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis
should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted use of
topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy, ie skin atrophy striae and
telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freeze. **Leg**
Category POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.80. PL 0426/0043. F
Prescribing information is available on request.

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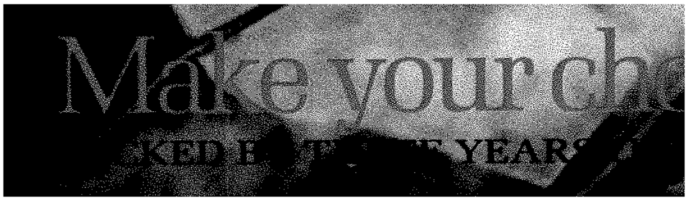
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A clear, colourless solution in a plastic dropper bottle. Glauline is available in three strengths containing 0.1%, 0.3% or 0.6% w/v metipranolol together with benzalkonium chloride 0.01% w/v as a preservative.

USES

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LEGAL CATEGORY

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PACKAGE QUANTITIES

Glauline is supplied as a sterile ophthalmic solution in a 5ml plastic dropper bottle.

FURTHER INFORMATION

Glauline has little or no effect on pupil size or accommodation.

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Reference 1. Kralian LM, American Journal of Optometry and Physiological Optics 1986; **63** (No. 4): 304-308.

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British Journal of Ophthalmology, 1988, **72**, 299–302

Computerised axial tomography and magnetic resonance scanning in the Tolosa-Hunt syndrome

D J B THOMAS, M C CHARLESWORTH, F AFSHAR, AND D J GALTON

From the Department of Medicine, Radiology, and Neurosurgery, St Bartholomew's Hospital, London EC1

SUMMARY A 50-year-old Asian male presented with a left sixth nerve palsy, left temporal pain, and rapidly deteriorating visual acuity in the left eye. A high resolution CT scan and magnetic resonance scan showed a left retro-orbital enhancing lesion extending from the lateral margin of the cavernous sinus on to the greater wing of the sphenoid and into the left orbit. Arteriography was normal. On high dose steroid therapy there was total resolution of the lesion. The value of imaging techniques in this condition is discussed.

The Tolosa-Hunt syndrome is a rare but well recognised cause of painful ophthalmoplegia[1] characterised by a granulomatous deposit in the region of the anterior cavernous sinus[2] which is usually steroid responsive. The position of this lesion makes histological confirmation difficult and dangerous, and as the differential diagnosis includes inflammatory vascular and neoplastic lesions[3] accurate imaging techniques are invaluable. CT scanning is of value in the diagnosis of this condition, but the appearances are not specific. This paper includes magnetic resonance scans, which have not previously been reported in this condition.

Case report

An Asian male aged 50 presented with a four-month history of diplopia and decreasing visual acuity which was preceded by three years of left-sided headaches. He dated the diplopia from an accident at work when some machine oil was splashed in his eye. The only past history was of a head injury three years prior to presentation. Physical examination revealed a left-sided sixth cranial nerve lesion with some proptosis on that side. Visual acuity was 6/6–9, and Goldmann perimetry was normal. There was reduced sensation to pinprick over the first branch of the trigeminal on the left.

Shortly after admission there was a rapid deterioration in the visual acuity of the left eye (from 6/6–9 to 6/36). He was immediately started on high-dose steroids (16 mg dexamethasone/day), which produced a dramatic improvement in visual acuity.

An initial high resolution IGE 9800 CT scan showed an enhancing lesion at the lateral margins of the cavernous sinus, the greater wing of the sphenoid, and extended into the orbit (Figs. 1A, 1B). The magnetic resonance (MR) scan showed slight proptosis of the left eye with a pseudotumour in the posterior part of the left orbit (Fig. 1C). Arterio-

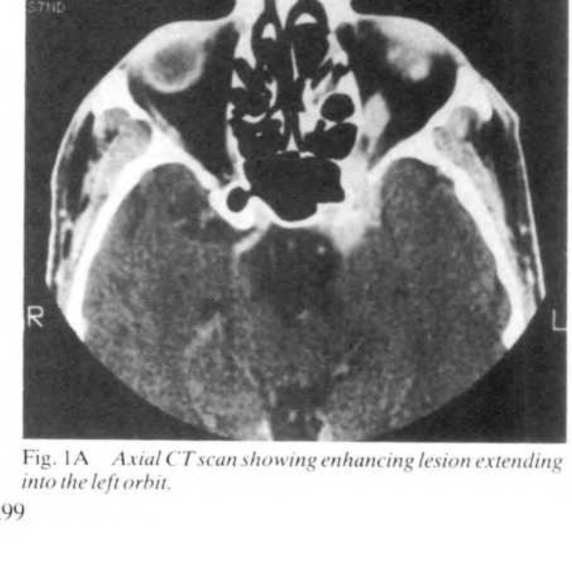


Fig. 1A *Axial CT scan showing enhancing lesion extending into the left orbit.*

Correspondence to Dr D J B Thomas, Mount Vernon Hospital, Northwood, Middlesex.

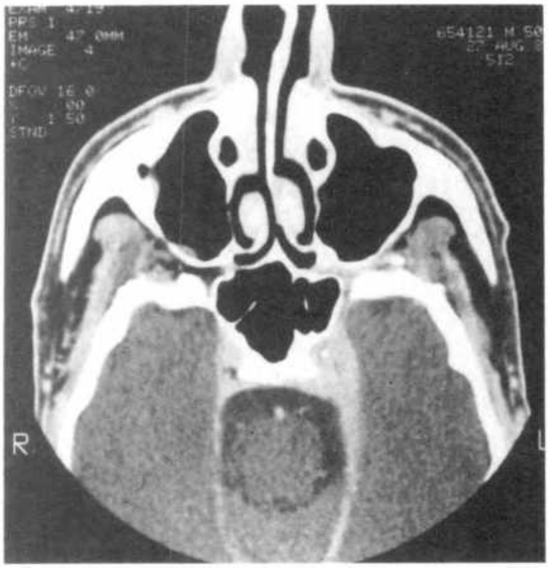


Fig. 1B *Axial CT scan showing marked distortion of cavernous sinus.*

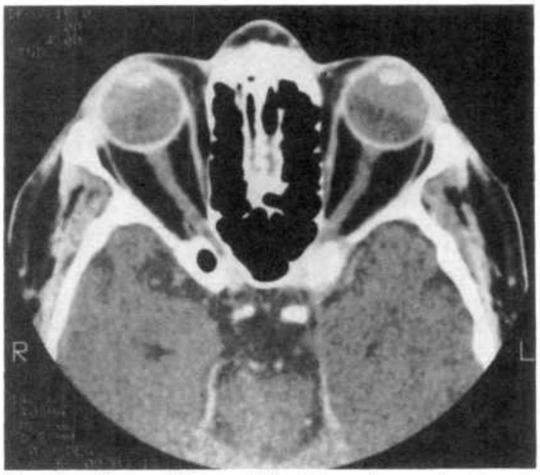


Fig. 2A *Repeat CT scan of Fig. 1A cut six months after steroid treatment.*

graphy was normal. High resolution CT and MR scans repeated six months after initiation of steroid treatment were normal (2A, 2B, 2C). Visual evoked responses (VER) from the left eye were compatible with a compressive lesion before steroids were started. There was normal latency, depressed amplitude, and distorted diphasic waveform. After six months on reducing steroid dosage the VER has returned to normal. High-dose steroid therapy was maintained for the whole of the four-month period. An early attempt to reduce steroids precipitated a marked deterioration in visual acuity. However, prolonged high-dose steroids resulted in a cushingoid appearance and marked proximal myopathy, and probably contributed to another admission to hospital, when the patient presented with an acute febrile illness, dyspnoea, and radiological evidence of diffuse bilateral pneumonia. The pneumonia responded to intravenous ampicillin and erythromycin, and the radiological appearance returned to normal. The only blood titres to change during this period were cytomegalovirus (from 1/64 to 1/1024). The patient is at present well and on a small dose of steroids.

Other investigations. Erythrocyte sedimentation rate, 10 mm in the first hour. Mantoux test −ve.

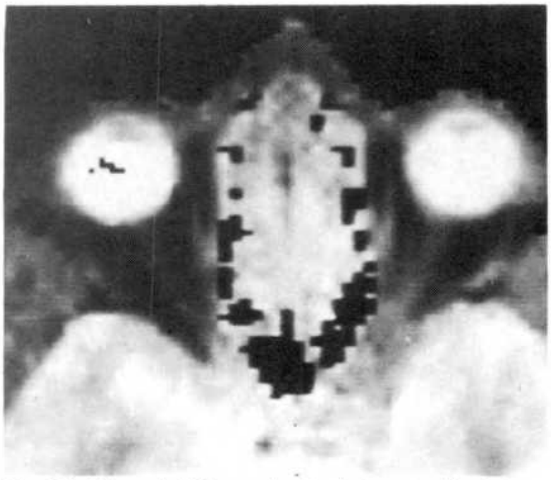


Fig. 1C *T1 mode MR scan showing lesion extending into left orbit.*

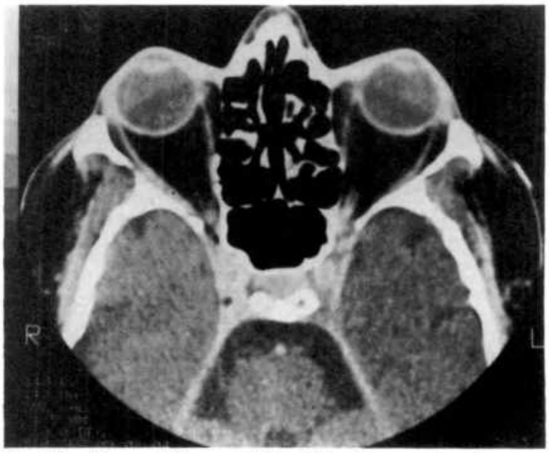


Fig. 2B *Repeat CT scan of Fig. 1B cut six months after steroid treatment.*

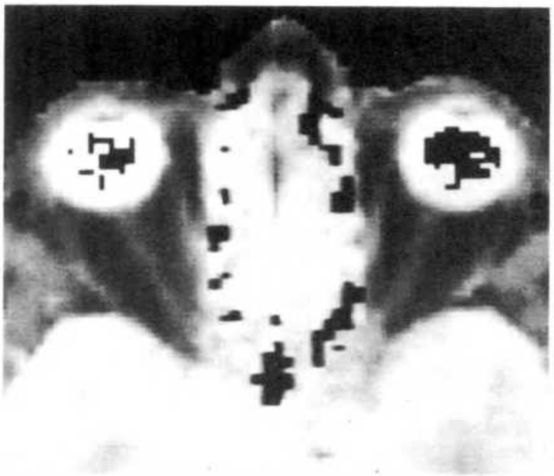


Fig. 2C *Repeat MR scan six months after steroid treatment.*

Kveim test −ve. Cerebrospinal fluid: protein 0·40 g/l, cells—1 mononuclear cell, cerebrospinal fluid glucose 3·5 mmol/l. VDRL test −ve. Bronchial biopsy normal.

METHODS

High-resolution CT scanning was carried out with the IGE 9800 using 2 mm cuts. Scans were taken in the axial plane and reconstructed in the coronal and sagittal planes. 150 ml of iohexol (Omnipaque) was used for contrast. Magnetic resonance scanning was carried out on the MD800 (0·80 Tesla resistive magnet scanner) in the axial plane on T1 mode (TR 1000 ms, T1+200 ms). The visual evoked response was performed with a standard checkerboard on full fields.

Discussion

In 1961 Hunt *et al.*[1] collected six cases with the following features. Gnawing retro-orbital pain which might precede the ophthalmoplegia and neurological involvement of any combinations of nerves passing through the cavernous sinus. The symptoms might last for days or weeks, and although spontaneous remission did occur there was sometimes residual deficit and attacks might recur subsequently. Earlier Tolosa[2] had reported on the histology from a patient with similar symptoms who had died. Histology showed a non-specific granulomatous lesion characterised by proliferative fibroblasts and by infiltration of the septa on the walls of the sinus with lymphocytes and plasma cells. Since then there have been sporadic reports of non-specific histology. Although the Tolosa-Hunt syndrome is a well recognised but rare cause of painful ophthalmoplegia, it remains a diagnosis of exclusion,[4] with many other lesions such as aneurysms, tumour and even diabetic microangiopathy being reported as mimicking it.[5]

When this syndrome was first recognised it was not possible to obtain direct views of the anterior cavernous sinus, and indirect procedures such as orbital venography and angiography were necessary. CT scanning has now made it possible to visualise this lesion accurately but the appearances are non-specific. However, they are invaluable in monitoring the responses to treatment. Magnetic resonance tomography is a non-invasive method for soft tissue imaging, and, as the images are not degraded by bone, it provides an excellent technique for visualising bony structures such as the orbit. The main factors influencing soft tissue contrast in magnetic resonance are proton density (PD), proton spin lattice relaxation time (T1), and spin-spin relaxation time (T2). The last two constants describe the exponential return to equilibrium of proton magnetisation after excitation. The structures of the normal orbit are easily recognised because of the contrast provided by orbital fat. This has a high proton content and short relaxation time, which makes it appear black on T modes. The lens also appears black, and the coats of the eye are contrasted against the vitreous, which is white because of its slow relaxation time. Orbital bone is not seen on T images. Intraorbital tumours such as metastatic carcinoma or lymphoma appear grey on the T image, and, although the appearance for carcinoma is the same on the PD image, that for lymphoma may appear white. Smith *et al.*[6] have reported two orbital pseudotumours due to presumed inflammatory change which also appear grey on the T image, and this is similar to the magnetic resonance scan appearance in our patient. Pseudotumours appear less well delineated than real tumours, and there is no bone erosion. The virtual disappearance of the lesion after steroid treatment makes it likely to be a steroid responsive inflammatory disease.

Although histological examination is desirable, the inaccessibility of the lesion makes the procedure difficult and hazardous. In the past attempts at biopsy have been associated with high morbidity and mortality.[7] Recently a new technique has been described, in which a fine needle is directed under CT guidance.[4] This appears to have been most successful in the user's hands diagnosing unsuspected aspergillosis, but has not been used widely outside that unit.

There are several interesting points in the patient's response to treatment and the clinical course of the disease. The subject was a middle-aged Asian who presented with a sixth nerve lesion, headache, and rapidly deteriorating visual acuity. It has been suggested that this condition is common in patients of Asian descent, but this is disputed.[8] There was a dramatic response to high-dose steroid therapy, with rapid clearing of pain and improvement of vision. The diplopia has been slow to improve and still has not entirely disappeared. It is interesting that the patient continually mentions strange colour perception and abnormalities of vision, which have persisted in spite of normal visual evoked responses, visual acuities, and Goldmann perimetry. Some patients with the Tolosa-Hunt syndrome have abnormalities of contrast sensitivity which are not identified by conventional visual function tests. The precise mechanism for this remains obscure, but it has been suggested the lesion is due to damage to large fast-conducting fibres which project from the retinal ganglion to magnocellular layers of the lateral geniculate ganglion.[9]

Although cases of Tolosa-Hunt syndrome may remit spontaneously, in general they require treatment with steroids and are very steroid sensitive. Pain is the most responsive symptom and usually disappears within 48 hours of high-dose steroid treatment. Some authors have suggested this could be used as a therapeutic trial because results are so consistent.[10] In our patient high levels of dexamethasone were required (16 mg per day), and this resulted in profound proximal myopathy with a cushingoid facies. However, there was no worsening of the patient's mild diabetes or hypertension. Finally the presumed cytomegalovirus pneumonia was probably related to steroid induced immunosuppression, though it has been reported in healthy persons.[11]

References

1 Hunt WE, Meagher JN, Lefever HE, Zerman Z. Painful ophthalmoplegia: its relation to indolent inflammation of the cavernous sinus. *Neurology* 1961; **11:** 56–62.
2 Tolosa E. Periarteriotic lesions of the carotid siphon with clinical features of a carotid infra-clinoidal aneurysm. *J Neurol Neurosurg Psychiatry* 1954; **19:** 300–2.
3 Lahke J. Superior orbital fissure syndrome. *Arch Neurol* 1962; **7:** 289–300.
4 Rowed DW, Kassel EE, Lewis AJ. Transorbital intracavernous needle biopsy in painful ophthalmoplegia. *J Neurosurg* 1985; **62:** 776–80.
5 Jabs DA, Miller NR, Green WR. Ischaemic optic neuropathy with painful ophthalmoplegia in diabetes mellitus. *Br J Ophthalmol* 1981; **65:** 673–8.
6 Smith FW, Cherryman GR, Singh AK, Forrester JV. Nuclear response tomography of the orbit at 3·4 MHz. *Br J Radiol* 1985; **58:** 947–57.
7 Dornan TL, Espir LE, Gale EAM, Tattersall RS. Remittent painful ophthalmoplegia: and Tolosa-Hunt syndrome. *J Neurol Neurosurg Psychiatry* 1979; **42:** 270–5.
8 Spillane JD. The geography of neurology. *Br Med J* 1972; ii: 506–12.
9 Fallowfield LJ, Rees JE. Psychophysical assessment of a patient with Tolosa-Hunt syndrome. *J Neurol Neurosurg Psychiatry* 1983; **46:** 576–8.
10 Mathew NT, Chandy J. Painful ophthalmoplegia. *J Neurol Sci* 1970; **11:** 243–56.
11 Idell S, Johson M, Beauregard L, Leamur N. Pneumonia associated with rising cytomegalovirus antibody titres. *Thorax* 1983; **38:** 957–8.

Accepted for publication 10 February 1987.

British Journal of Ophthalmology, 1988, **72,** 303–304

Angioid streaks in beta thalassaemia minor

FRANK P KINSELLA AND DAVID J MOONEY

From the Research Unit of the Royal Victoria Eye and Ear Hospital, Dublin

SUMMARY We report what we believe to be the first recorded case of angioid streaks in a patient with beta thalassaemia minor. The occurrence of angioid streaks in a patient with a relatively normal iron balance and only very mild haemolysis may be explained by the combination of pregnancy with associated multiple transfusions in a myopic patient where an inherent defect in Bruch's membrane may exist.

Angioid streaks, representing breaks in Bruch's membrane, with the typical ophthalmoscopic appearance of reddish brown bands radiating outwards from the optic disc, were first described in 1889 by Doyne.[1] Subsequently they have been described in a number of conditions, the most notable being pseudoxanthoma elasticum,[2] Paget's disease of bone,[3] and certain haemoglobinopathies, particularly sickle cell disease.[4,5]

We report a patient with beta thalassaemia minor who was found to have angioid streaks in both fundi.

Case report

In July 1982 a 42-year-old woman of Italian extraction had beta thalassaemia minor diagnosed by a haematological unit, having presented with a long history of mild anaemia with more severe exacerbations needing multiple blood transfusions during each of three preceding pregnancies (the last one being in 1973). Apart from symptoms of mild anaemia she was otherwise asymptomatic, and general physical examination was normal. There was no family history of thalassaemia.

In February 1986 she presented with a three-month history of blurred vision in her left eye. Examination revealed a visual acuity of 6/60 in the right eye and 2/60 in the left eye, improving to 6/18 and 6/36 respectively with −3·50 dioptre sphere correction in each eye. Angioid streaks were noted in both fundi, radiating outwards from the optic discs and passing through both maculae (Figs. 1 and 2).

Laboratory investigations were as follows: Hb 11·5 g/dl, mean cell volume 61 μm^3 reticulocyte count 3% (normal less than 2%). The following were normal: serum Fe, total iron binding capacity, serum folic acid, serum B_{12}, erythrocyte folic acid, haptoglobins, and thyroxine. Hb electrophoresis showed Hb A=94·7%, Hb A2=5·3% (normal less than or equal to 2%). A blood film showed occasional microcytic hypochromic red blood cells in addition to rod, pear, and target cells; leucocytes and platelets were normal.

A skin biopsy showed no evidence of pseudoxanthoma elasticum, nor was there any evidence, clinical, biochemical, or radiological, of Paget's disease of bone.

Over a four-year follow-up the haemoglobin remained fairly constant (between 10 to 11 g/dl) with only a very mild haemolysis (as shown by haematological indices) while the patient received no treatment.

Discussion

Angioid streaks have been described in several haemoglobinopathies, including homozygous sickle cell anaemia,[4] sickle cell trait,[6] sickle cell haemoglobin C disease,[7] and sickle cell thalassaemia,[8,9] but until recently their occurrence in the thalassaemias has not been described (Table 1). In 1979 angioid streaks were noted in a patient with haemoglobin H

Table 1 *Angioid streaks in the thalassaemias*

Type	*Reported cases*	*Authors*
Haemoglobin H disease	1	Daneshmend[10]
Beta thalassaemia major	1	Gibson *et al.*[11]
	1	Theodossiadis *et al.*[12]
Beta thalassaemia intermedia	1	Singerman[13]
Beta thalassaemia minor (our report)		

Correspondence to Mr David Mooney, Royal Victoria Eye and Ear Hospital, Adelaide Road, Dublin 2, Ireland.

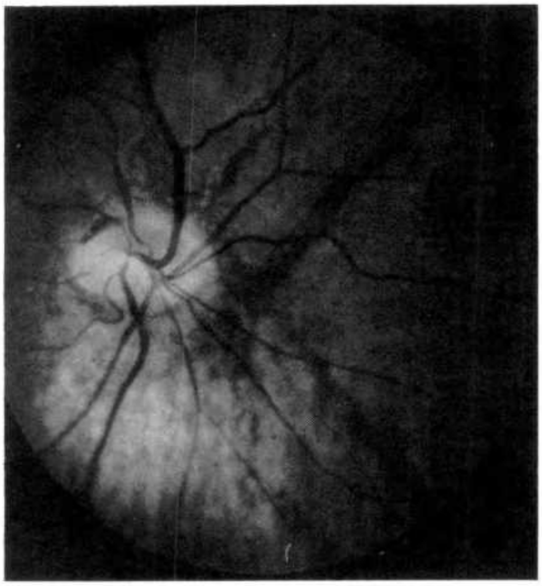


Fig. 1 *Fundus photograph of right optic disc showing angioid streaks.*

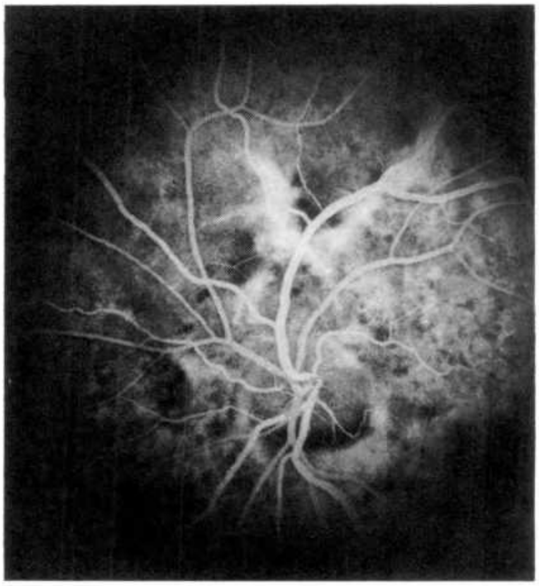


Fig. 2 *Fluorescein angiogram of left fundus demonstrating angioid streaks above optic disc.*

disease[10] (an alpha thalassaemia), and their occurrence in two cases of beta thalassaemia major[11,12] and in one of beta thalassaemia intermedia[13] has since been reported. We now report a case of beta thalassaemia minor in which angioid streaks were observed.

Unlike the earlier reported cases of beta thalassaemia major and intermedia, which had iron overload syndromes (from serial blood transfusions for anaemia), our patient was in a normal or slightly negative state of iron balance, with only very low grade haemolysis.

The pathogenesis of angioid streaks in the haemoglobinopathies is uncertain and may be due to either inherent defects or chronic iron deposition in Bruch's membrane—though this latter explanation has recently been disputed.[14] A possible explanation for the occurrence of angioid streaks in our patient with a relatively normal iron status and very mild haemolysis is that iron deposition in Bruch's membrane occurred during the repeated pregnancy-associated transfusions in a myopic patient in whom a defect in Bruch's membrane may already have existed.

References

1 Doyne RW. Choroidal and retinal changes—the results of blows to the eyes. *Trans Ophthalmol Soc UK* 1889; **9:** 128–31.

2 Goodman RM, Smith EW, Paton D, *et al.* Pseudoxanthoma elasticum: a clinical and histopathological study. *Medicine* 1963; **42:** 297–332.

3 Terry TL. Angioid streaks and osteitis deformans. *Trans Am Ophthalmol Soc* 1934; **32:** 555–73.

4 Goodman G, von Sallmann L, Holland MG. Ocular manifestations of sickle cell disease. *Arch Ophthalmol* 1957; **58:** 655–82.

5 Condon PI, Serjeant GR. Ocular findings in elderly cases of homozygous sickle cell disease in Jamaica. *Br J Ophthalmol* 1976; **60:** 361–4.

6 Gerde LS. Angioid streaks in sickle cell trait haemoglobinopathy. *Am J Ophthalmol* 1974; **77:** 462–4.

7 Condon PI, Serjeant GR. Ocular findings in haemoglobin SC disease in Jamaica. *Am J Ophthalmol* 1972; **74:** 921–31.

8 Goldberg MF, Charache S, Acacio I. Ophthalmologic manifestations of sickle cell thalassemia. *Arch Intern Med* 1971; **128:** 33–9.

9 Condon PI, Serjeant GR. Ocular findings in sickle cell thalassemia in Jamaica. *Am J Ophthalmol* 1972; **74:** 1105–9.

10 Daneshmend TK. Ocular findings in a case of haemoglobin H disease. *Br J Ophthalmol* 1979; **63:** 842–4.

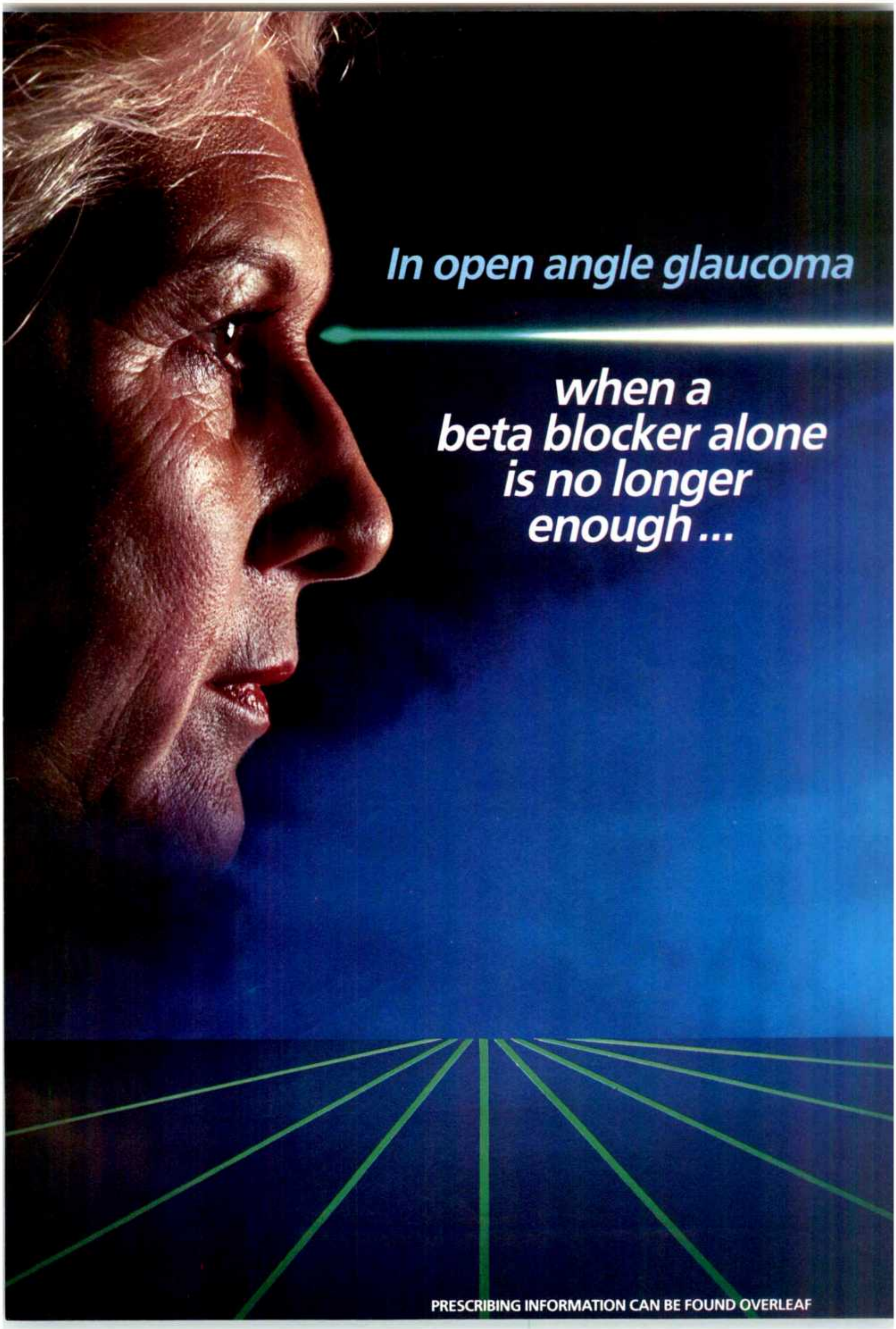
11 Gibson JM, Raychaudhuri P, Rosenthal AR. Angioid streaks in a case of beta thalassaemia major. *Br J Ophthalmol* 1983; **67:** 29–31.

12 Theodossiadis G, Ladas I, Koutsandrea C, Damanakis A, Petroutsos G. Thalassaemia et neovaisseaux sous—rétiniens maculaires. *J Fr Ophtalmol* 1984; **7:** 115–8.

13 Singerman LJ. Angioid streaks in thalassaemia major. *Br J Ophthalmol* 1983; **67:** 558.

14 Hamilton AM, Pope FM, Condon PI, *et al.* Angioid streaks in Jamaican patients with homozygous sickle cell disease. *Br J Ophthalmol* 1981; **65:** 341–7.

Accepted for publication 20 February 1987.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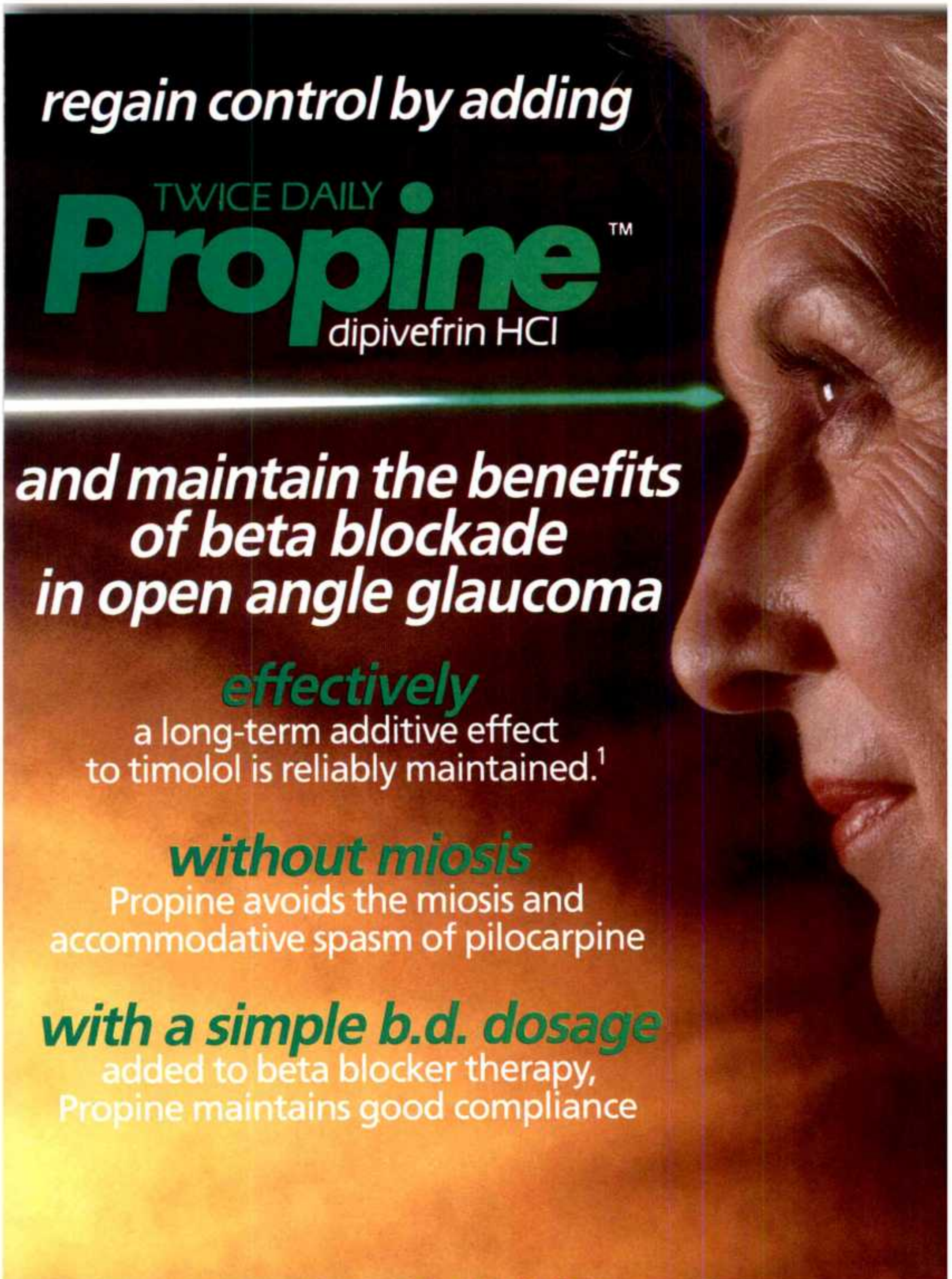

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British Journal of Ophthalmology, 1988, 72, 305–308

Cyclic esotropia in a patient with unilateral traumatic aphakia: case report

M D COLE, A HAY, AND E M EAGLING

From the Birmingham and Midland Eye Hospital

SUMMARY Cyclic esotropia is a rare and poorly understood condition normally treated by correcting the deviation measured on the squinting day. Control in some patients with this condition can be gained by correcting their refractive errors, thereby improving acuity. We report on an adult patient who developed cyclic esotropia after unilateral traumatic aphakia with failed contact lens wear whose squint was corrected by secondary intraocular lens implantation. This may be explained by the reduction in the degree of aneisokonia which subsequently improved stereopsis.

Cyclic esotropia is a rare and poorly understood disorder of ocular motility. Since the first report in 1958,[1] many patients have been described. Other names for this condition are alternate day, or clock mechanism, esotropia.[2] It has also been called circadian esotropia,[3] but this does not accurately describe the condition correctly, as the word circadian means a daily or 24 hour change. Costenbader and Mousel[4] reviewed 3500 squint cases and found three that exhibited cyclical recurrence.

In most patients[2] the condition occurs in childhood. On 'straight days' no anomalies of binocular vision are observed, though heterophoria may be present; on 'strabismic days' a large-angle esotropia will appear and sensory anomalies are often found. Diplopia is rare, and fusional amplitudes determined with the synoptophore are defective or absent. A 48-hour cycle is encountered most commonly, but 72-hour and 96-hour cycles have been reported. The cyclic nature of the strabismus may last from four months to several years, after which the cycle breaks and esotropia becomes constant.

Surgery based on the amount of heterotropia as it occurs on the squinting days has been eminently successful in permanently curing this condition and re-establishing normal binocular functions.[5]

This report describes an adult patient with uniocular traumatic aphakia who subsequently developed cyclic esotropia. The squint was cured by capsulotomy and secondary intraocular lens implantation.

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Case report

A 24-year-old maintenance engineer first presented in November 1976 with an intraocular foreign body in his left eye from hammering a piece of machinery. The particle had penetrated the cornea and lens and was located posteriorly; it was removed with the giant magnet via a pars plana approach. A traumatic cataract slowly developed, which was aspirated four months later, and the vision corrected to 6/9. He was fitted with a hard contact lens, which was worn for about a year but was subsequently abandoned.

He failed to keep any further appointments until October 1984, when he returned after noticing that his left eye turned in intermittently over the previous 12 months. He recognised that there was a definite pattern. On day 1 he would squint all day. This continued until approximately midday on the following day, when the eyes became straight. The eyes remained straight for the rest of that day and the whole of the following day, only for the pattern to restart one day later. He did not recognise any diplopia during the squinting periods when asked directly. He had no previous history of a squint or amblyopia, and there was no family history of a squint. The patient was found to be right handed and right footed for all tasks. The posterior capsule had thickened during the previous period of absence, so that the corrected visual acuity in the aphakic eye had deteriorated to <6/60. A capsulotomy with the Nd-YAG laser was performed. The subsequent orthoptic assessment was as follows:

In the squinting period (Fig. 1) the visual acuity

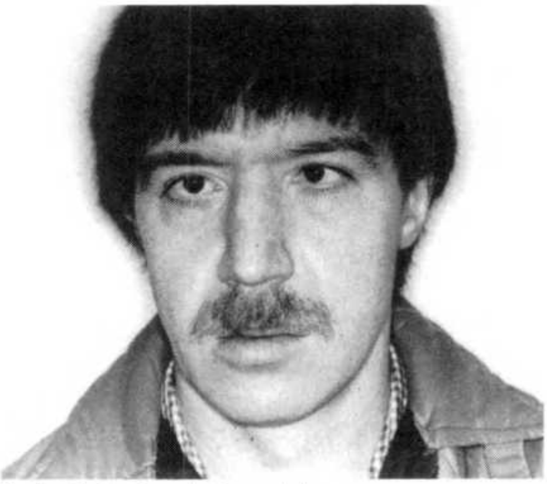


Fig. 1 *Patient in squinting period.*

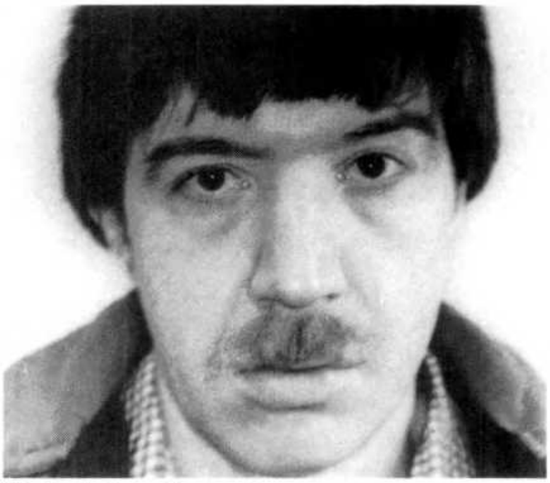


Fig. 2 *Patient without squint.*

was 6/4 in the right eye with no correction (the refractive error in this eye was +0·50 sph with +0·50 cyl at 180°) and 6/7·5 in the left with a +12 D sph lens (no near visual acuity was recorded). The cover test revealed a 50 PD (prism dioptre) left esotropia for near and distance and diplopia was recognised during the test. This was measured by the prism cover test and found to be 57 PD with a 2 PD right hypertropia. There was a full range of ocular movements. When the eyes converged the visual axes crossed and the two images could be joined. Further convergence caused the left eye to diverge.

Examination of the patient on the synoptophore showed that the objective angle was +29°. There was also a right hypertropia of 2 PD. With a +12 D sph lens in front of the left eye, the subjective angle was not recordable, as the image from the left eye was suppressed. There was no demonstrable fusion.

On the following afternoon (Fig. 2) the visual acuity was 6/4 (N5) in the right eye and 6/6 in the left with a +12 D sph lens (N10 with +15 D sph). The cover test showed no deviation for near and a left microesotropia of +2° to +3° for distance. There was a full range of ocular movements. Binocular convergence was present to 10 cm. The left eye then diverged resulting in diplopia.

Examination of the patient on the synoptophore with +12 D sph lens in front of the left eye showed that both the objective and subjective recording of the deviation was +4° with a right hypertropia of 1 PD. Fusion was demonstrable at 6°, showing a range of 10° of convergence and 4° of divergence. Simple stereopsis was appreciated, but the Wirt and Randot tests could not demonstrate this.

The patient was asked to keep a record of his squint. During the cycle he did not recognise any alterations in behaviour, mood, sleeping habits, temperature, frequency of micturition, libido, appetite, or sweating.

The visual acuity in his left eye was corrected with a soft contact lens to 6/12 (N8). This did not change the pattern of the squint, which remained the same for six months. The visual acuity in the right eye was 6/5 (N5). The pattern then started to become more variable. He sometimes spent periods of three to four days either straight or squinting. A V pattern became more apparent, and on the squinting days the esotropia measured 40 PD for distance and 25 PD for near.

Four months later the pattern had changed to a left esotropia of 3–4 days' duration. Although the patient was young and the eye traumatised, it was decided to carry out a secondary implantation of a 19·0 dioptre anterior chamber flexible loop intraocular lens. This was because his occupation made contact lens wear difficult. The operation was performed in January 1985, and the visual acuity in the left eye quickly improved to 6/9 (N8) unaided (this could be improved to 6/5 with −1·25 D sph). Postoperatively the squint became constant for 10 days, straightened for one day, then returned for one more day. The eye has remained straight ever since.

Six months later he is symptom free, with no complications. The orthoptic report is as follows.

The visual acuity in the right eye is 6/5 (N5) and in the left eye 6/6 (N6) unaided. The cover test reveals a small esophoria for near and distance with rapid recovery. There is a full range of eye movements; binocular convergence is present to 6 cm. The left eye subsequently diverges, resulting in diplopia. The esophoria when measured by the prism cover test is 2 PD for near and 1 PD for distance. The prism fusion range is 30 PD base out, and 10 PD base in for near; and 25 PD base out, and 4 PD base in for distance. Stereopsis has a resolution of 240″ of arc when measured with the TNO (random dot stereogram) test.

Ocular examination found the lens nicely positioned in the anterior chamber with a clear central gap in the posterior capsule. The intraocular pressures, optic discs, and fundi were normal.

Discussion

Cyclic esotropia is a strabismus which is present on one day and absent on the next and so on, thus showing a 48-hour cycle.[2] It is unrelated to visual acuity, accommodation, fatigue, and non-fusion. It is usually accompanied by suppression and poor binocular vision. Helveston[6] outlined the characteristics of a typical patient (Table 1). He recorded only one adult aged 32.

Variations in the timing of the cycle are common, and the cycle often becomes more prolonged with time. Our patient was atypical, though, in that he recognised diplopia during the cover test in the squinting period. This may be because the squint developed in adulthood, and binocular vision developed normally in childhood. It is also unusual to demonstrate a manifest deviation at all in the so called non-squinting period.

Consecutive cyclic esotropia has been recorded,[7,8] and there has been one reported case of cyclic hypertropia.[3] Troost *et al.*[9] recorded an adult case following retinal detachment surgery. Both our patient and the one reported by Troost *et al.*[9] developed the squint after a disturbance of acuity in one eye sometime after the event. Apart from the operations involved there appear to be no other precipitating factors. No previous history or family history of a squint existed. The visual acuity in Troost and colleagues' patient was restored to normal.[9] There was a cyclical pattern of pupillary dilatation on the affected side which persisted when the squint appeared along with a blepharoptosis. These changes were thought to be due either to a periodic sympathetic hyperactivity during the esotropic day or to some cyclic oculomotor nerve dysfunction.

Table 1 *Average characteristics of cyclic esotropia*

Onset	Three to four years
Deviation	30 to 40 PD (prism dioptres) esotropia
Vertical incomitance	Mild V pattern
Refraction	With or without 2·25 D sph hypermetropia
Vision	With or without amblyopia
AC/A ratio	May be high
Response to glasses	May fuse with glasses (with or without bifocals)
Response to surgery	Usually fuses after surgery
Usual cyclic pattern	48 Hours

Helveston[6] commented on the similarity between cyclic esotropia and a decompensated accommodative squint. Windsor and Berg[3] thought that cyclic esotropia represented a slow motion development of a concomitant squint. However, these all refer to childhood cases.

Kubuta and Harada[10] believe that the essential characteristic of cyclic esotropia is a sixth nerve palsy. They demonstrated this by electromyography. Williams and Normandin[11] presented a case of a 7-year-old child who was struck by a car and rendered unconscious. He subsequently developed a bilateral sixth-nerve palsy with a cyclic esotropia.

24-Hour cycles are well known in medicine.[12] However, our understanding of the cyclic mechanism remains speculative. It is known that some children show regular 48-hour cycles in body temperature, pulse rate, and other physiological functions. In adults, alternate-day cycles may show in changes in behaviour, moods, or physiological functions, including depression, schizophrenia, or sleep patterns. Transition between phases tend to be sharp 'as if a switch has been thrown'.[12] They may follow head trauma, high fever, cerebrovascular disease, syphilis, or encephalitis. Richter[12] points out that the appearance of these cycles in psychiatry is always secondary to the presence of a basic illness. Work with rats has shown that lesions in the hypothalamus may disrupt the clock mechanism. Richter postulated that in man the superior colliculi or the oculomotor nuclei could be defective. He suggests that patients with cyclic esotropia have a more deeply rooted biological abnormality than is apparent by their squint alone—that is, the squint may be the only outward manifestation of a more basic disturbance. The supposition is strengthened by previous observation in a small number of patients. Thus, in-phase changes in behaviour have been reported by Chamberlain[13] in one patient and Roper-Hall and Yapp[14] in six. The latter investigators also noticed electroencephalographic (EEG) changes in two patients and increased frequency of micturition in one patient during the squinting phase. Investigation of various biological parameters including psychological tests, serial EEGs, urinary excretion products, pulse rate, body temperature, urine volume, and frequency of micturition by Friendly *et al.*[15] in one patient and similar studies performed by Roper-Hall in collaboration with Yenner failed to reveal a more deeply rooted 48-hour clock mechanism. A child with minimal brain dysfunction who developed cyclic esotropia was also investigated by Gadroth *et al.*[16] to assess the hypothalamic-pituitary axis and the sleep cycle, but no abnormal function was detected.

Roper-Hall and Yapp[14] also noticed that in three out of eight of these patients there was incomplete or unusual cerebral dominance. A strong family history is often observed. In our patient on direct questioning no behavioural or physiological changes mentioned above were observed. He consistently preferred to use his right hand and foot for all tasks.

Surgery based on the full amount of heterotropia as it occurs on the day of squinting has been successful in permanently curing the condition. This success favours the hypothesis that these patients are basically strabismic, and by some unknown mechanism capable of maintaining normal binocular vision during the cycle. Various authors[3-5 13 14] have reported successful results with this form of treatment.

Helveston[6] collected 13 patients by sending a questionnaire to 61 ophthalmologists with an interest in strabismus. He found five patients who had been treated successfully by correcting their refractive error (two patients had a high accommodative convergence/convergence (AC/A) ratio requiring bifocals). So it seems that improving acuity or reducing the accommodation in those with high AC/A ratios can help the patient to control the squint. However, treatment of patients with amblyopia by occlusion has tended to convert the squint into a permanent esotropia.

This case is unique in that the improvement in acuity from 6/12 (N8) to 6/6 (N6) in the left eye, and reduction of aneisokonia by secondary lens implantation in an aphakic eye, have corrected the squint. The image size magnification with the aphakic eye corrected with a contact lens is approximately 8%, whereas the magnification with an intraocular lens is negligible.[17] It would appear that the resultant improvement in stereopsis has re-established binocular control in a patient presumed to have developed normal binocular vision in childhood.

The trigger zone causing cyclic esotropia could be located in a number of anatomical sites. It may lie within the oculomotor nuclei or their interconnections,[12] or it may lie within the sensory pathways that effectively control the oculomotor nuclei. In view of the response to treatment the trigger in this patient must lie within the sensory pathways. The prior development of normal binocular vision may be required to establish control by this method.

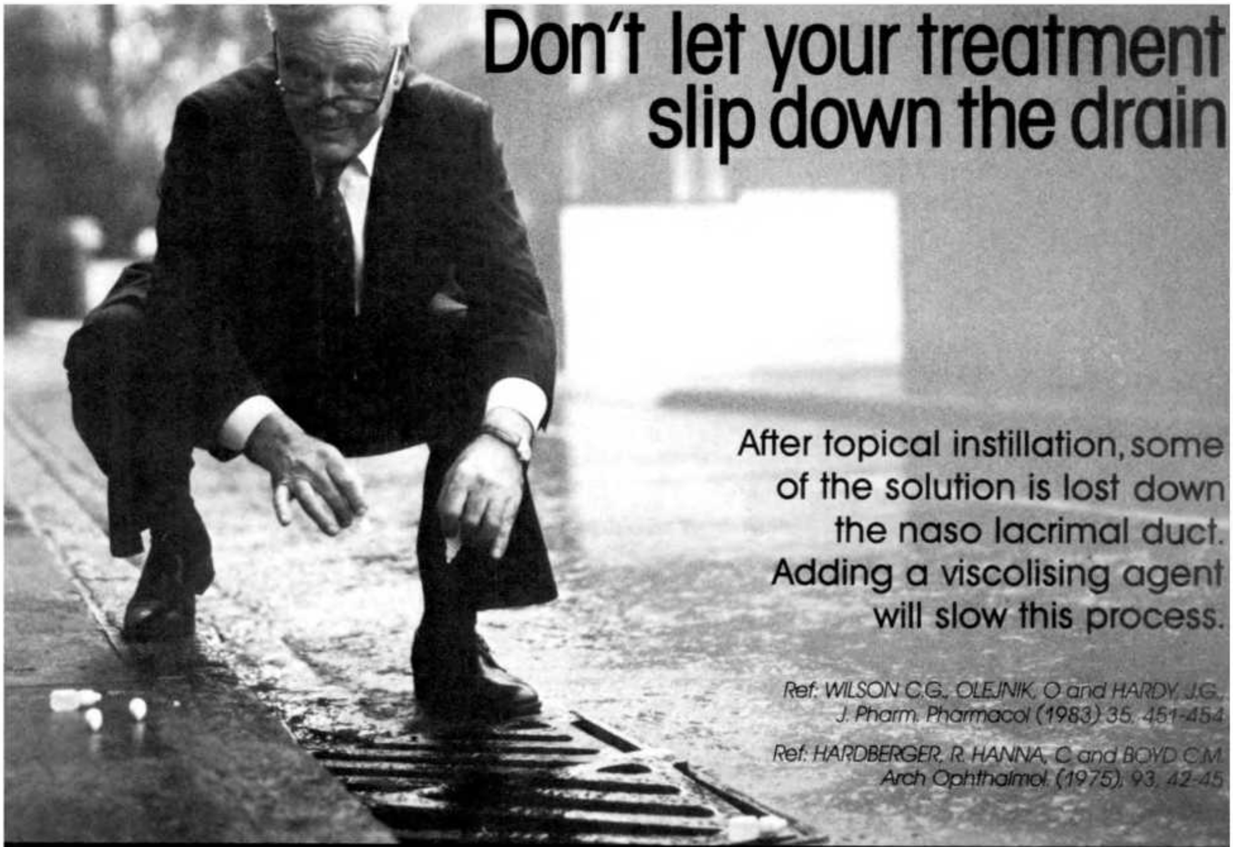
In conclusion, if uniocular acuity or binocular vision can be improved in patients with cyclic esotropia, this should be attempted before resorting to conventional squint surgery.

The authors thank K R Whale, E A Howrie, and H E Willshaw for constructive criticism of this paper.

References

1 Burian HM. Round table discussion. In: Allen JH, ed. *Strabismic ophthalmic symposium*. St Louis: Mosby, 1958: 488.
2 Von Noorden GK. *Binocular vision and ocular motility*. Toronto: Mosby, 1985: 385–6.
3 Windsor CE, Berg EF. Circadian heterotropia. *Am J Ophthalmol* 1981; **91:** 8–13.
4 Costenbader FD, Mousel DK. Cyclic esotropia. *Arch Ophthalmol* 1964; **71:** 88–9.
5 Helveston EM. Surgical treatment of cyclic esotropia. *Am Orthopt J* 1976; **26:** 87–8.
6 Helveston EM. Cyclic strabismus. *Am Orthopt J* 1973; **23:** 48–51.
7 Uemura Y, Tomita M, Tanaka Y. Consecutive cyclic esotropia. *J Pediatr Ophthalmol Strabismus* 1977; **14:** 278–80.
8 Munchnick RS, Sanflippo S, Dunlap EA. Cyclic esotropia developing after strabismus surgery. *Arch Ophthalmol* 1976; **94:** 459–61.
9 Troost BT, Abel L, Noreika J, Genovese FM. Acquired cyclic esotropia in an adult. *Am J Ophthalmol* 1981; **91:** 8–13.
10 Kubota N, Harada M. Cyclic esotropia. *Nippon Ganka Gakkai Zasshi* 1962; **68** (suppl): 297–302.
11 Williams F, Normandin V. Case study: traumatic bilateral lateral rectus muscle paresis vs. traumatic cyclic esotropia. *Am Orthopt J* 1976; **26:** 102–3.
12 Richter CP. Clock-mechanism esotropia in children. *Bull Johns Hopkins Hosp* 1968; **122:** 218–23.
13 Chamberlain W. Cyclic esotropia. *Am Orthopt J* 1968; **18:** 31–4.
14 Roper-Hall MJ, Yapp JMS. Alternate day squint. In: Kimpson H, ed. *First International Congress of Orthoptics*. St Louis: Mosby, 1968: 262–71.
15 Friendly DS, Manson RA, Albert DG. Cyclic strabismus—a case report. *Doc Ophthalmol* 1973; **34:** 189–202.
16 Gadoth N, Dickerman Z, Lerman M, Lavie P. Cyclic esotropia with minimal brain dysfunction. *J Pediatr Ophthalmol Strabismus* 1981; **18:** 14–6.
17 Wilensky J. Intraocular lens. In: Peyman GA, Sanders DR, Goldberg MF, eds. *Principles and practice of ophthalmology*. Philadelphia: Saunders, 1980: 634–6.

Accepted for publication 10 February 1987.



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Immunological analysis of the aqueous humour in candida endophthalmitis. I: Experimental study

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SUMMARY An immunological study of aqueous humour and serum was carried out in experimental ocular candidosis in rabbits. Anti-candida antibody titres, immunoglobulin G, and albumin levels were evaluated in the aqueous humour and in the serum. A local synthesis of anti-candida antibodies was detected in numerous rabbits at the height of clinical activity of the lesions.

In 1954 Goldmann and Witmer[1] proposed that ocular toxoplasmosis could lead to the intraocular production of antibodies. Subsequent experimental studies have supported their concept of intraocular antibody production.[2] Various investigators have suggested localised specific antibody production in ocular toxocariasis,[3] in herpes ocular infection,[4] and in acute retinal necrosis.[5] Our research team questioned whether in candida endophthalmitis an analogous ocular immune response could be detected. We studied anti-candida antibody titres in aqueous humour of rabbits with experimentally induced ocular candidosis.

Materials and methods

Materials. Fifteen New Zealand white 4-month-old female rabbits were used. A *Candida albicans* haematogenous endophthalmitis was provoked by the methods described by Edwards *et al.*[6] 0·1 ml of a suspension of *Candida albicans* ($3·1\times10^6$ organisms/ml, yeast phase, 20 h culture) in brain heart infusion was injected into the marginal ear vein. The strain was isolated from a vitreous sample of a patient with candida endophthalmitis. A fundus examination was performed daily during the first week, then weekly over a period of two months. This examination was done after maximum dilatation following instillation of phenylephrine and tropicamide, with the indirect ophthalmoscope (Schepens) using the 20 dioptre lens (Nikon). The number of ocular lesions was established and a qualitative description of the fundus was noted.

Methods. Blood samples and bilateral anterior chamber taps were performed in each rabbit before inoculating the strain, on the 10th day following injection and weekly thereafter until the 42nd day. Aqueous humour aspiration was performed under topical anaesthesia by inserting a 27 gauge needle through the limbus and aspirating approximately 0·2 ml of aqueous humour into an insulin syringe. All samples were stored at −20°C until used.

To determine whether an intraocular synthesis occurred it was necessary to evaluate the anti-candida antibody titres and the immunoglobulin G levels in the aqueous humour and in the serum. An albumin measurement was also taken to determine the condition of the blood aqueous barrier.

Serum and aqueous humour anti-candida antibodies were analysed by indirect immunofluorescence according to the Ambroise-Thomas technique.[7] After 48 hours' culture in Sabouraud medium, *Candida albicans* organisms were used to coat glass slides and were then incubated on the same slides with dilutions of serum or aqueous humour samples (dilutions being continually halved, starting from 1:40 for the sera, and with a pure sample for the aqueous humour). After being washed they were stained with a goat anti-rabbit immunoglobulin fluorescein conjugated antibody (Cappel) diluted to 1:50 with Evans blue for counterstaining. Each test series included a hyperimmune serum for positive control as well as a negative control, both analysed under the same conditions.

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Serum and aqueous humour albumin and immunoglobulin G concentrations were analysed by laser immunonephelometry (Behring). For the albumin determination 100 µl of a 1:1600 diluted serum or 1:10, 1:20, 1:100 (where necessary) diluted aqueous humour was incubated 15 minutes with 200 µl of specific antibody (goat anti-rabbit albumin (Cappel)) 1:6 diluted. For the immunoglobulin G evaluation 20 µl of a 1:160 diluted serum or 1:2, 1:10, 1:100 diluted aqueous humour was incubated for 30 minutes with 200 µl of a goat anti-rabbit immunoglobulin G (Cappel) 1:6 diluted. In both cases concentrations were determinated by comparison with dilutions of a standard rabbit serum analysed simultaneously under the same experimental conditions.

C coefficient. As the presence of candida antibodies in the aqueous humour could be due either to a transudation of serum antibodies in the anterior chamber through the blood aqueous barrier,[7] or to local synthesis, we calculated the C coefficient according to a formula derived by Desmonts.[8]

$$C = \text{antibody titres}\,\frac{\text{aqueous humour}}{\text{serum}} \times \text{globulin G}\,\frac{\text{serum}}{\text{aqueous humour}}.$$

This coefficient, which compares the immunity quotient of the aqueous humour with that of the serum, enables us to evaluate the local synthesis of specific antibodies. In theory a titre greater than 1 suggests local antibody production within the eye. In interpreting the results we followed Desmonts' formula,[9] considering negative a coefficient less than 2, significant a C from 2 to 4, and positive a C greater than 4.

Results

CLINICAL EVALUATION

Twelve rabbits of the 15 inoculated developed chorioretinitis, six bilateral, 6 unilateral. The lesions appeared to be identical to those of human candida endophthalmitis. The initial chorioretinal lesions were observed after one week. They were either unique or multiple, white, spherical, small (approximately 1/2 disc diameter) located on the surface of the retina. Three weeks after inoculation the lesions increased in size, and they were accompanied by overlying vitreous haze. After two months there was a massive vitreous exudation and chorioretinal and vitreous cultures were positive.

The control group comprised the six uninfected eyes in the rabbits showing unilateral disease; no lesions were found on ophthalmoscopic examination, and vitreous cultures were negative.

BIOLOGICAL EVALUATION

After completion of the analysis of all aqueous humour and serum samples taken at different dates the results obtained at days 0, 10, and 34 seemed particularly significant.

Rabbits with endophthalmitis

Day 0 (Table 1): Specific anti-candida antibodies were not detected in the aqueous humour or serum specimens.

Day 10 (Table 2): A significant increase in immunoglobulin G and albumin was observed in the aqueous humour, accompanied by development of specific antibodies in both serum and aqueous humour. The C coefficient was significant in only 15% of cases.

Day 34 (Table 3): Albumin and immunoglobulin G concentrations remained elevated. An increase in specific antibody titres in the serum was noted and more particularly a clear increase of these antibodies in the aqueous humour with a positive C coefficient in 58% of cases.

Results from day 17 were comparable to those at day 10. By day 26 the coefficient was already significant or positive in 40% of cases.

On day 42 no differences were observed compared to day 34 results.

Control eyes

Despite the significant increase in specific antibodies in the serum, anti-candida antibody titres in the aqueous humour remained nil or weak, with a C coefficient less than one in all cases. Albumin and immunoglobulin G levels in the aqueous humour were not modified.

Discussion

In the controls' eyes numerous cases showed a coefficient of 0 or less than 1. This finding points to the reproducibility of our tests.

In the affected eyes at the early stages of clinical lesions we found anti-candida antibodies in the aqueous humour in the majority of rabbits. Also noted was a very significant elevation of albumin level in the aqueous humour—indirect evidence of a damaged blood ocular barrier due to inflammation. The negativity of the C coefficient may be explained by the absence or mere beginning of a local synthesis, or by a masking of local production by a leak of serum antibodies through the blood ocular barrier.

At the height of clinical activity of the lesion a clear increase of anti-candida antibodies is noted in the aqueous humour, resulting in a positive C coefficient in many cases. In those situations where the C coefficient is negative, the serum reveals a very high titre of specific antibodies, probably masking local production.

Our experimental study enabled us to identify, as

Table 1 *Anti-candida antibodies, immunoglobulin G, and albumin detected in serum and aqueous humour of eyes with candida endophthalmitis before inoculation. (1) Antibody titres, (2) expressed as a percentage in relation to standard serum*

	Anti-candida antibodies (1)		*Immunoglobulins G (2)*		*Albumin (2)*		*C coefficient*
	AH	*Serum*	*AH*	*Serum*	*AH*	*Serum*	
Eye 1	0	0	0·3	68	0·5	118	0
Eye 2	0	0	0·3	80	0·5	138	0
Eye 3	0	0	0·7	65	1·2	114	0
Eye 4	0	0	0·4	78	0·7	111	0
Eye 5	0	0	0·4	70	0·9	109	0
Eye 6	0	0	0·3	60	0·8	126	0
Eye 7	0	0	0·3	96	0·8	135	0
Eye 8	0	0	0·1	96	0·9	135	0
Eye 9	0	0	0·1	101	1·1	133	0
Eye 10	0	0	0·1	101	0·9	133	0
Eye 11	0	0	0·8	100	0·9	111	0
Eye 12	0	0	0·9	100	1·1	111	0

AH=aqueous humour.

Table 2 *Anti-candida antibodies, immunoglobulin G, and albumin detected in serum and aqueous humour of eyes with candida endophthalmitis 10 days after inoculation. (1) Antibody titres, (2) expressed as a percentage in relation to standard serum*

	Anti-candida antibodies (1)		*Immunoglobulins G (2)*		*Albumin (2)*		*C coefficient*
	AH	*Serum*	*AH*	*Serum*	*AH*	*Serum*	
Eye 1	4	40	18	70	29	109	0·34
Eye 2	4	40	19	78	37	124	0·8
Eye 3	16	320	3	77	6	110	1
Eye 4	2	80	11	80	28	118	0·18
Eye 5	64	640	12	70	24	114	0·6
Eye 6	32	640	3·4	68	6·2	126	1
Eye 7	2	40	1·5	96	2·6	126	3
Eye 8	2	40	1·3	96	1·9	126	3·7
Eye 9	1	40	5	91	10	108	0·4
Eye 10	1	40	2·7	91	4·3	108	0·8
Eye 11	40	40	58	93	75	100	1·6
Eye 12	40	40	45	93	82	100	2

AH=aqueous humour.

Table 3 *Anti-candida antibodies, immunoglobulin G, and albumin detected in serum and aqueous humour of eyes with candida endophthalmitis 34 days after inoculation. (1) Antibody titres, (2) expressed as a percentage in relation to standard serum*

	Anti-candida antibodies (1)		*Immunoglobulins G (2)*		*Albumin (2)*		*C coefficient*
	AH	*Serum*	*AH*	*Serum*	*AH*	*Serum*	
Eye 1	128	320	6	75	12	114	4·8
Eye 2	8	160	2	86	4	131	2
Eye 3	128	320	5·5	77	8	111	7
Eye 4	320	160	34	83	74	108	4·8
Eye 5	64	640	9	81	13	116	1
Eye 6	64	640	13	63	24	93	0·5
Eye 7	64	160	7·5	90	13	113	4·8
Eye 8	64	160	6·6	91	12	113	5·5
Eye 9	64	640	6·4	85	11	126	1·3
Eye 10	32	640	3·7	85	5·6	126	1
Eye 11	640	80	59	87	90	107	11·8
Eye 12	320	80	44	87	87	107	7·9

AH=aqueous humour.

in ocular toxoplasmosis, a local synthesis of specific antibodies in cases of candida chorioretinitis. This production may be observed only a few days after the onset of the clinical lesions. Another interesting finding is the significant damage to the blood ocular barrier. These results have led us to believe that an anterior chamber tap could be used as a diagnostic procedure in human candida endophthalmitis.

References

1 Goldmann H, Witmer R. Antikörper in kammerwasser. *Ophthalmologica* 1954; **127:** 232–330.

2 Silverstein AM. Doyne memorial lecture 1974. Immunogenic uveitis. *Trans Ophthalmol Soc UK* 1974; **94:** 496–516.

3 Felberg NT, Shields JA, Federman JL. Antibody to *Toxocara canis* in the aqueous humour. *Arch Ophthalmol* 1981; **99:** 1563–4.

4 Denis J, Rossignol A, Langlois M, Dorey C, Aymard M, Giraud JP. Valeur du coefficient de charge immunitaire des globulines de l'humeur aqueuse au cours de l'herpès oculaire. *J Fr Ophtalmol* 1981; **4:** 173.

5 Sarkies N, Gregor Z, Forsey T, Darougar S. Antibodies to herpes simplex virus type I intraocular fluids of patients with acute retinal necrosis. *Br J Ophthalmol* 1986; **70:** 81–4.

6 Edwards JE, Montgmerie JZ, Foos RY, Shaw K, Guze LB. Experimental hematogenous endophthalmitis caused by *Candida albicans*. *J Infect Dis* 1975; **131:** 649–57.

7 Ambroise-Thomas P. Immunofluorescence indirecte. In: Golvan Y, Ambroise-Thomas P, eds. *Nouvelles techniques en parasitologie*. Paris: Flammarion, 1984: 181–4.

8 Desmonts G. Definite serological diagnosis of ocular toxoplasmosis. *Arch Ophthalmol* 1966; **76:** 839–51.

9 Desmonts G. Toxoplasmose oculaire. Etude épidemiologique. Bilan de 2030 examens d'humeur aqueuse. *Arch Ophtalmol (Paris)* 1973; **83:** 87–102.

Accepted for publication 29 January 1987.

British Journal of Ophthalmology, 1988, **72**, 313–316

Immunological analysis of the aqueous humour in candida endophthalmitis. II: Clinical study

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SUMMARY An anterior chamber paracentesis was carried out on six patients with candida endophthalmitis and on control subjects. We endeavoured to find out if there was local production of antibodies by evaluating the anti-candida antibody titres, the immunoglobulin G, and the albumin levels in the aqueous humour and in the serum. A significant difference in the level of specific antibodies between patients and controls was found. Local synthesis of anti-candida antibodies was discovered in five out of six patients with candida endophthalmitis. There would seem to be a correlation between the severity of uveitis and antibody titres.

Over the last two years the number of cases of candida endophthalmitis in Europe has increased, especially among heroin addicts.[1] While the clinical ocular findings are quite typical, in order to be absolutely sure of the diagnosis it is necessary to recover the candida from the vitreous body. However, this procedure at times proves unsuccessful. We therefore carried out anterior paracentesis on six patients presenting symptoms of candida endophthalmitis to determine whether local production of antibodies was present in the aqueous humour.

Materials and methods

Patients. Our study was carried out by comparing two groups of subjects: patients with candida endophthalmitis and control patients.

The six patients with candida endophthalmitis are described below.

CASE 1

A 21-year-old woman, a drug addict, complained of blurred vision. Her visual acuity was finger counting at 3 feet (1 m) (OD and OS). A dense cellular reaction was observed in the anterior chamber and in the vitreous. It was associated with a massive vitreous exudation in both eyes. The fundus examination, difficult to perform, revealed in each eye a paramacular white mass extending into the vitreous. Blood cultures were negative. Candidosis serological results were: immunofluorescence 1:320; haemagglutination 1:20480; immunoelectrophoresis against *Candida albicans* antigenic extract 6 precipitin lines. Scalp culture revealed *Candida albicans* colonies.

CASE 2

A 33-year-old man developed bilateral blindness following neurosurgery. Examination revealed severe anterior uveitis in both eyes as well as considerable vitreous organisation, making fundus examination impossible. Blood cultures were negative. Candidosis serological results were: immunofluorescence 1:80; haemagglutination 1:320; immunoelectrophoresis against *Candida albicans* antigenic extract 1 precipitin line.

CASE 3

A 28-year-old man, a drug addict, consulted us for decrease of visual acuity in the left eye. Ocular examination revealed left side visual acuity of 1/10, severe anterior uveitis with many iris lens synechiae, and dense hyalitis obscuring retinal detail. The right eye was normal. Candidosis serological results were: immunofluorescence 1:160; haemagglutination 1:320; immunoelectrophoresis against *Candida albicans* antigenic extract 3 precipitin lines. Attempts to

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recover candida organisms from the blood and scalp were unsuccessful.

CASE 4
A 39-year-old man suffered from a candida septicaemia induced by intestinal perforation owing to sigmoid diverticulitis. The ocular symptoms developed one month later while he was convalescing. His visual acuity was obviously normal. The left eye had grade 1+ cells in the anterior chamber and two exudative retinal lesions in the posterior pole. His right eye was normal on examination. Candidosis serological results were: immunofluorescence 1:320; haemagglutination 1:160; immunoelectrophoresis against *Candida albicans* antigenic extract 5 precipitin lines. Attempts to recover candida organisms from the blood and scalp were unsuccessful.

CASE 5
A 21-year-old man, a drug addict, presented with decreased visual acuity in the right eye. Ophthalmic examination revealed a visual acuity of 1/10, a Tyndall light phenomenon in the anterior chamber (1+ cells), a choroiditis paramacular lesion with local vitreous haze, and macular oedema. A search for candida from the scalp was negative. Candidosis serological results were: immunofluorescence 1:320; haemagglutination 1:20 480; immunoelectrophoresis against *Candida albicans* antigenic extract 2 precipitin lines. Blood cultures yielded many *Candida albicans* colonies.

CASE 6
A 30-year-old woman, a drug addict, had a visual acuity of 8/10 in both eyes with a normal anterior segment. A fundus examination revealed two white, round, jutting paramacular lesions. Scalp culture yielded *Candida albicans* colonies. Blood cultures were negative. Candidosis serological results were: immunofluorescence 1:320; haemagglutination 1:160; immunoelectrophoresis against *Candida albicans* antigenic extract 2 precipitin lines.

The control group consisted of 14 patients (six males and eight females) undergoing routine cataract extraction or retinal detachment surgery. Their mean age was 42 years, range 24 to 72 years. All these patients had raised serum anti-candida antibody titres—above 80 by immunofluorescence, above 160 by haemagglutination, or at least 1 precipitin line in immunoelectrophoresis.

Methods. The same immunological studies were performed on the patients suffering from candida endophthalmitis as on the control group. In each patient in order to determine whether intraocular synthesis occurred it was necessary to evaluate the anti-candida antibody titre and the IgG level in the aqueous humour and in the serum. All the investigations were performed according to the methods described in the experimental study (anti-candida antibodies were analysed by indirect immunofluorescence according to Ambroise-Thomas[2]). Serum and aqueous humour albumin and immunoglobulin G concentrations were analysed by laser immunonephelometry Behring). The only differences were: for immunofluorescence a goat antihuman immunoglobulin conjugated antibody (bioMérieux) was diluted to 1:100; for albumin analysis sera were diluted to 1:2000; aqueous humour was diluted to 1:10. For IgG analysis serum was diluted to 1:200, and aqueous humour was tested undiluted. In both cases concentrations were determined by comparison with dilutions of a standard human serum (standard protein Behring) analysed simultaneously under the same experimental conditions.

C coefficient. As the presence of candida antibodies in the aqueous humour could be due either to a transudation of serum antibodies in the anterior chamber through the blood aqueous barrier, or to local synthesis, we calculated the C coefficient as we did in the experimental candida endophthalmitis.

In interpreting the results we followed Desmonts' formula,[3] considering negative a C coefficient less than 2, significant a C from 2 to 4, and positive a C greater than 4.

Results

The results of aqueous humour and serum samples obtained from patients with candida endophthalmitis are presented in Table 1. Anti-candida antibodies were found in the aqueous humour of five patients. Concentrations in all patients of albumin and immunoglobulin G were high in the aqueous humour. The C coefficient was positive in three cases, significant in two cases, and negative in one. In the patients with a positive coefficient there was very intense anterior segment inflammation. Two other patients with slight local production showed less serious anterior uveitis. The only patient with a normal anterior segment presented no local production of antibodies.

The results of immunological studies in the control group are presented in Table 2. Despite raised anti-candida antibody titres in the serum of each patient, specific antibodies were found in the aqueous humour in only seven patients. All cases showed a C coefficient equal to or less than 1.

Discussion

Clinical examination may make us fairly certain of

Table 1 *Results of tests on the aqueous humour and the serum: patients with candida endophthalmitis*

Biological data	*Patients*						
	1		*2*	*3*	*4*	*5*	*6*
	Before cure	*After cure*					
Immunoglobulin G							
Aqueous humour (mg/l)	410	25	68	240	50	24	12·7
Serum (mg/l)	18270	11510	9300	12870	14800	16890	15050
Albumin							
Aqueous humour (mg/l)	2050	220	206	1200	475	95	100
Serum (mg/l)	32290	40220	36280	32610	41430	43800	42900
Candida antibodies							
Aqueous humour (titre)	32	No antibody	8	20	2	Positive not diluted	No antibody
Serum (titre)	320	80	80	160	320	320	320
C coefficient	4·5	No local production	13·6	7	2	2	No local production

the presence of candida endophthalmitis. But confirmation depends on biological tests. However, recovering candida from an extraocular sample is by no means easy; in addition the interpretation of serological results causes some difficulty. In any case, neither a positive extraocular cultured site nor a serology suggesting recent visceral candidosis allows us to hold the candida organism responsible for the uveitis. Recovering candida organism from the eye is the only proof that candida infestation has actually occurred. Culture of aqueous humour[4-6] has never revealed candida except in the case of an aphakic patient.[7] However, a vitreous tap[8 9] or a vitrectomy[5 10 11] does enable the collection of the candida organism. Recovering candida from the vitreous cavity is thus the best diagnostic method, though it may at times prove unsuccessful. In fact, vitreous tap is not always positive,[10 12] and vitrectomy may be negative despite concentration of the specimens, particularly after antifungal treatment.[14] Thus anterior chamber paracentesis, while presenting only presumptive diagnostic evidence, seems to be an interesting technique. Testing for production of intraocular specific antibodies by anterior chamber paracentesis can be used to diagnose uveitis caused by toxoplasmosis,[3] herpes,[13] and *Toxocara canis.*[14] So far as we know it has never been used to confirm a diagnosis of candida endophthalmitis.

Immunological tests of the aqueous humour in candida endophthalmitis appear to be helpful. In fact numerous control studies have shown good reproducibility of these tests. Testing for local produc-

Table 2 *Results of tests on the aqueous humour and the serum: control patients*

	Anti-candida antibodies		*Immunoglobulin G*		*Albumin*		*C Coefficient*
	AG (titre)	*Serum (titre)*	*AH (mg/l)*	*Serum (mg/l)*	*AH (mg/l)*	*Serum (mg/l)*	
Patient 1	0	80	74	10440	620	32190	0
Patient 2	0	160	25	11410	210	34940	0
Patient 3	1	160	15	7280	148	36320	0·3
Patient 4	0	80	30	11240	224	46020	0
Patient 5	1	160	93	15020	130	32250	1
Patient 6	0	80	26	9260	260	31680	0
Patient 7	1	160	110	10620	489	31790	0·6
Patient 8	0	80	20	11020	150	33150	0
Patient 9	1	160	80	12450	540	50700	0·9
Patient 10	0	80	40	11430	180	37390	0
Patient 11	1	160	120	10140	502	42990	0·5
Patient 12	1	160	73	11250	250	41250	0·9
Patient 13	0	80	40	16800	205	47700	0
Patient 14	1	160	105	11234	512	35420	0·6

AH=aqueous humour.

tion of anti-candida antibodies has enabled us to express strong support for the diagnosis of ocular candidosis in five out of six patients.

Moreover, it would seem to be justifiable to note that the more severe the anterior inflammation, the more revealing the anterior chamber paracentesis actually is. Testing for local production of anti-candida antibodies has shown different immune responses: some of the results were significant, while others were only slightly positive or even negative. The last result may be explained either by a leak of specific serum antibodies through the blood–eye barrier which has been modified by inflammation, or by a tap performed too soon, as suggested by the results of our experimental study.

References

1 Sorrel TC, Dunlop C, Collignon PJ, Harding JA. Exogenous ocular candidosis associated with intravenous heroin abuse. *Br J Ophthalmol* 1984; **68:** 841–5.

2 Ambroise-Thomas P. Immunofluorescence indirecte. In: Golvan Y, Ambroise-Thomas P, eds. *Nouvelles techniques en parasitologie*. Paris: Flammarion, 1984: 181–4.

3 Desmonts G. Toxoplasmose oculaire. Etude épidémiologique. Bilan de 2030 examens d'humeur aqueuse. *Arch Ophtalmol (Paris)* 1973; **83:** 87–102.

4 Barthelemy F, Offret H, Saragoussi JJ, Pouliquen Y, Dhermy P. Toxicomanies et endophtalmies à *Candida albicans*: problèmes diagnostiques et thérapeutiques. *J Fr Ophtalmol* 1981; **4:** 637–46.

5 Elliot JH, O'Day DM, Gutow GS, Podgorski SF, Akrabawi P. Mycotic endophthalmitis in drug abusers. *Am J Ophthalmol* 1979; **88:** 66–72.

6 O'Connor GR. Uveitis and the immunologically compromised host. *N Engl J Med* 1978; **299:** 130–2.

7 Robertson DM, Ricley FC, Hermans PE. Endogenous candida oculomycosis. *Arch Ophthalmol* 1974; **91:** 33–8.

8 Forster RK, Zachary IG, Cottingham AJ, Norton WD. Further observations on the diagnosis, cause, and treatment of endophthalmitis. *Am J Ophthalmol* 1976; **81:** 52–6.

9 Rowsey JJ, Newsom DL, Sexton DJ, Harms WK. Endophthalmitis: current approaches. *Ophthalmology* 1982;. **89:** 1055–66.

10 Aguilar GL, Blumenkrantz MS, Egbert PR, McCulley JP. Candida endophthalmitis after intravenous drug abuse. *Arch Ophthalmol* 1979; **97:** 96–100.

11 Snip RC, Michels RG. Pars plana vitrectomy in the management of endogenous endophthalmitis. *Am J Ophthalmol* 1976; **82:** 699–704.

12 Le Rebeller MJ, Lagoutte F, Dupuy P. Endophtalmie à *Candida albicans* chez les heroïnomanes. *Bull Soc Fr Ophtalmol* 1981; **11:** 917–22.

13 Denis J, Rossignol A, Langlois M, Dorey C, Aymard M, Giraud JP. Valeur du coefficient de charge immunitaire des globulines de l'humeur aqueuse au cours de l'herpès oculaire. *J Fr Ophtalmol* 1981; **4:** 173.

14 Felberg NT, Shields JA, Federman JL. Antibody to *Toxocara canis* in the aqueous humor. *Arch Ophthalmol* 1981; **99:** 1563–4.

Accepted for publication 29 January 1987.

British Journal of Ophthalmology, 1988, **72**, 317

Correspondence

Is radiation a justifiable treatment of choroidal melanoma?

Sir, The paper by W A Manschot and R van Strik (*Br J Ophthalmol* 1987; **71:** 348–52) is of value as it stimulates thinking about the controversies in melanoma treatment, but it lacks important relevant data.

The concept of tumour doubling time of the authors is an oversimplification, as they assume that there is only one growth potential of all tumour cells involved, whereas in fact a tumour consists of a heterogeneous group of cells of different growth potential.[1]

The statement that the tumour death rate of all patients with melanomas in the <7 mm diameter group is nil is incorrect. One patient out of 42 patients of Thomas *et al.*[2] had metastases. Barr *et al.*[3] mention metastatic death in one patient with a 7×7×2 mm melanoma. Davidorf and Lang[4] had no metastatic deaths in their series of only 18 patients. Metastatic death occurred in three of the 22 patients with a choroidal melanoma up to 7 mm diameter and 2 mm in height, Tla according to the TNM classification, from the Leiden University Eye Clinic. Statistical evaluation may not be justifiable in these low numbers but it proves that even in Tla size tumours metastatic death occurs.

The authors state that tumour regression of 50% or 75% after radiation only delays metastatic death but that only total regression may save patients' lives. This is not true, as, especially after irradiation of large melanomas, a totally necrotic residual mass may persist.[5] Fig. 1 shows one of five cases of the University Eye Clinic in Essen. After ruthenium-106 application to a choroidal melanoma the height of the tumour regressed from 8·4 to 6·3 mm only. Because of a rather intense post-treatment inflammatory reaction attributed to tumour necrosis[6] the eye having light perception only was enucleated three months after the irradiation. Histopathology, however, revealed a completely necrotic tumour mass without any viable cells (Figs. A, B).

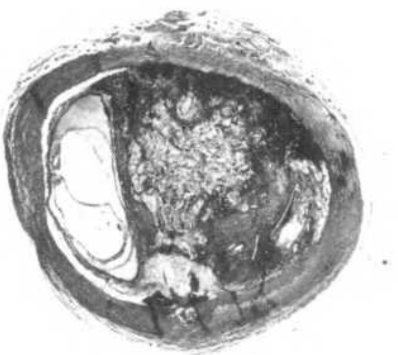

Fig. 1A *Overview of a histological section through a totally necrotic tumour in an eye after ruthenium applicator treatment performed in the University Eye Clinic in Essen. Intense post-treatment inflammatory reaction necessitated enucleation.*

The authors state that in almost all histopathologically studied eyes enucleated after radiotherapy viable tumour cells were present. The finding of viable tumour cells on histopathology in the enucleated eye after irradiation is what could be expected, as tumour growth after radiotherapy is one of the main reasons for performing enucleation. The fact that only in a few cases viable tumour cells could not be found indicates that in the postradiation follow-up patients have been carefully controlled and that hardly any errors have been made by mistakingly enucleating eyes with melanomas which have properly regressed. Moreover, after irradiation the tumour may be 'sterilised,' containing viable cells which, however, do not enter mitosis any more. This information has already been given to Manschot by Char[7] in his answer to a letter to the editor by Manschot:[8] 'The major effect of radiation is to destroy the tumour's reproductive integrity. In successfully radiated animal models, histologically normal intermitotic cells can remain in situ for a long period. DNA-induced errors result in cell death mainly after cell enters mitosis. After successful ocular irradiation, usually some residual necrotic or sterile cells remain.'

Concerning metastatic death the authors mention only unfavourable results of radiotherapy as compared with enucleation, but ignore all the more favourable results. They elaborate on the results of Gass,[9] who found a much higher metastatic death after cobalt-60 irradiation than after enucleation, but omit to mention that the statistical reappraisal Gass had made of his results led to the conclusion 'that after adjusting for both size and location, the treatments were almost significantly different using a likelihood ratio test. This leads to the conclusion that the issue of which treatment is better for the patient is still not settled.'[10]

The authors have failed to mention results of several other long-term studies with a follow-up period of more than four years as advocated by them. Augsburger *et al.*[11] in an observational study of 237 patients with posterior uveal melanomas, 74·7% of whom were followed-up for five years or longer, 140 having been treated with enucleation and 97 with cobalt plaque radiotherapy, found after statistical adjustment for intergroup differences in risk factors that the difference in effect of enucleation versus cobalt plaque therapy on survival time was not statistically significant.

After cobalt-60 plaque irradiation of 123 patients Hungerford (personal communication, 1987) found no difference statistically in metastatic death from the comparable group of patients treated by enucleation after an observation period of 10 to 20 years.

Lommatzsch[12] evaluated the results of 188 patients with choroidal melanomas treated with Ru-106 applicators followed up for more than five years with a mean period of 9·4 years. Of this group 18 (9·6%) had died from metastases. These results and the survival rate after irradiation of 79·5% (death only from metastases) after 10 years confirmed his earlier results[13] that the survival rate after local beta irradiation is higher than after enucleation of tumours of a comparable size.[14]

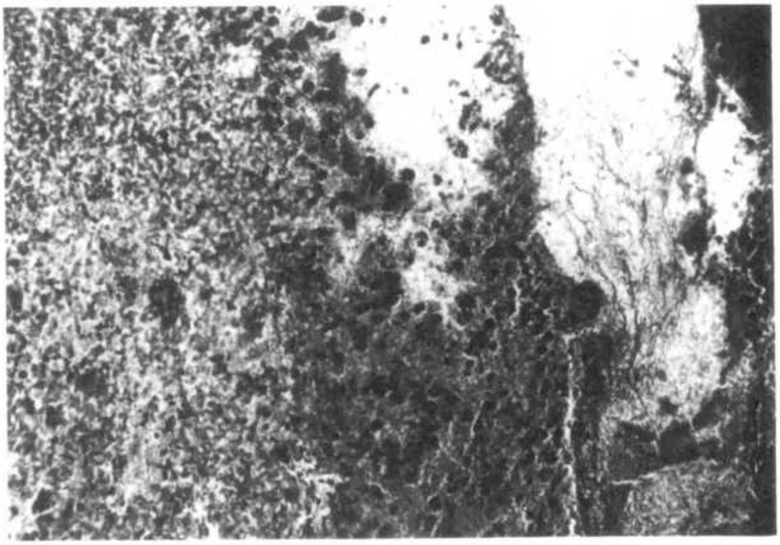

Fig. 1B *Detail of depigmented section of the same eye. On the left side the solid part of the necrotic tissue shows ghost images of tumour cells. In the middle cell debris and melanophages are seen. On the right side part of a large blood vessel which lost its endothelial cells contains only fibrin. ×96. Histopathological processing was performed in the pathology laboratory of the Erasmus University in Rotterdam.*

Gragoudas *et al.*[6] studied metastatic death in their first 128 patients after proton beam irradiation for melanoma of the choroid and/or ciliary body; all patients but one had been followed up for more than four years, the mean follow-up being five years. Metastases developed in 26 patients (20·5%); according to the Kaplan-Muir curve the five-year survival rate is 80%±5%. This compares favourably with the statistics after enucleation, as Jensen[16] in his extensive study of tumours of all sizes found a five-year metastatic death rate of 37%. This difference is the more remarkable as more than half of the proton beam treated tumours were large, with a diameter of >15 mm, having a more unfavourable metastasis prognosis than the unselected material of Jensen.[16]

The results of the long-term studies may not allow definite proof that the rate of metastasis is lower after irradiation than after enucleation, but the data obtained until now at least provide the reassurance that the long-term studies do not show a superiority of enucleation over irradiation as regards survival rate. Therefore irradiation of a choroidal melanoma is medically justifiable and a recommended treatment for patients with choroidal melanomas. We feel that every patient has not only the right to enucleation but also to radiotherapy within the limits of the different types of irradiation.

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References

1 Howes Jr EL. Basic mechanism in pathology. In: Spencer WH, ed. *Ophthalmic pathology. An atlas and textbook*. Philadelphia: Saunders, 1985; **i:** 90–1.

2 Thomas JV, Green WR, Maumenee AE. Small choroidal melanomas. A long term follow-up study. *Arch Ophthalmol* 1979; **97:** 861–4.

3 Barr CC, Sipperley JO, Nicholson DH. Small melanomas of the choroid. *Arch Ophthalmol* 1978; **96:** 1580–2.

4 Davidorf FH, Lang JR. The natural history of malignant melanoma of the choroid: small vs large tumors. *Ophthalmology* 1975; **79:** OP 313–20.

5 Goodman DF, Char DH, Crawford JB, Stone RD, Castro JR. Uveal melanoma necrosis after helium ion therapy. *Am J Ophthalmol* 1986; **101:** 643–5.

6 Gragoudas ES, Seddon JM, Egan K, *et al.* Long-term results of proton beam irradiated uveal melanomas. *Ophthalmology* 1987; **94:** 349–53.

7 Char DH. Reply to WA Manschot in a letter to the Editor. *Br J Ophthalmol* 1985; **99:** 616–7.

8 Manschot WA. Therapeutic options in uveal melanoma. Letter to the Editor. *Br J Ophthalmol* 1985; **99:** 615–6.

9 Gass JDM. Comparison of prognosis after enucleation vs cobalt 60 irradiation of melanomas. *Arch Ophthalmol* 1985; **103:** 916–23.

10 Gass JDM. In reply to letter to the Editor by Seddon *et al.* *Arch Ophthalmol* 1986; **104:** 176.

11 Augsburger JJ, Gamel JW, Sardi VF, Greenberg RA, Shields JA, Brady LW. Enucleation vs cobalt plaque radiotherapy for malignant melanomas of the choroid and ciliary body. *Arch Ophthalmol* 1986; **104:** 655–61.

12 Lommatzsch PK. Results after β-irradiation (106-Ru/106-Rh) of choroidal melanomas: 20 years' experience. *Br J Ophthalmol* 1986; **70:** 844–51.

13 Lommatzsch PK. β-Irradiation of choroidal melanoma with 106-Ru/106-Rh applicators. 16 years' experience. *Arch Ophthalmol* 1983; **101:** 713–7.

14 Kiehl H, Kirsch I, Lommatzsch P. Das Ueberleben nach Behandlung des malignen Melanoms der Aderhaut: Vergleich von konservativer Therapie (106-Ru/106-Rh Applikator) und Enukleation ohne und mit postoperativer Orbitabestrahlung,

1960 bis 1979. *Klin Monatsbl Augenheilkd* 1984; **184:** 2–14.
15 Jensen OA. Malignant melanomas of the human uvea. 25-year follow-up of cases in Denmark, 1943-1952. *Acta Ophthalmol (KGL)* 1982; **60:** 161–82.
16 McLean IW, Foster WD, Zimmerman LE. Prognostic factors in small malignant melanomas of choroid and ciliary body. *Arch Ophthalmol* 1977; **95:** 48–58.

SIR, Thank you for allowing us the opportunity to reply to the letter by Oosterhuis *et al.* Perhaps, we may answer, one by one, the consecutive paragraphs.

Paragraph 1 (The paper...): We would have appreciated an exact enumeration of the 'important relevant data' which our paper was said to be lacking. It is not possible to reply to undefined imputations.

Paragraph 2 (The concept...): We have never assumed 'that there is only one growth potential of all tumour cells involved.' We are familiar with the fact that a tumour generally consists of a heterogeneous group of cells of different growth potential. In basic oncology, however, tumour doubling time is defined as the time necessary for a tumour to double its volume; growth potentials of the various tumour cells are not specifically distinguished therein.

Paragraph 3 (The statement...): We did not state that the tumour-death rate of all patients with melanomas in the <7 mm diameter group is nil. We stated that this rate had been nil in two American reports;[1 2] we also specifically mentioned the one patient in the series of 42 patients of Thomas *et al.*,[2] who had metastases. but had not yet died, and the patient described by Barr *et al.*[3] who had died from metastases. We carefully concluded: 'It seems reasonable to postulate that, in general, choroidal melanomas are unlikely to shed cell emboli before they have reached the 7 mm stage.'

Paragraph 4 with regard to the question of tumour regression and metastatic death. We in fact stated: 'regression two years after irradiation of even 50% or 75% of the original volume can only delay metastatic death by one or two doubling times and cannot prevent eventual death from metastases. Only total regression can save a patient's life, if metastases were absent before treatment.' Oosterhuis *et al.* say that 'this is not true' and, surprisingly, substantiate their criticism with a histopathological report which actually had been made by one of us (WAM). The specimen concerned a blind, painful eye, which had to be enucleated within four months after a ruthenium irradiation of a small uveal melanoma in the clinic of one of our critics (AW). The apparently excessive radiotherapy had caused severe necrosis of almost all intraocular tissue, including the melanoma. Oosterhuis *et al.* point specifically to the reported complete necrosis of the small melanoma, but they do not appear to be alarmed by the total loss of the eye.

Paragraph 5 (The authors state...): Taking credit for a necrotic melanoma in a subtotally necrotic inner eye appears equivalent to taking credit for the finding 'that only in a few cases viable tumour cells could not be found' in enucleated irradiated eyes. The major part of 27 most recently reported[4] histopathologically studied irradiated eyes had not been enucleated because of continuing or relapsing tumour growth but because of postirradiation damage. The passage on the carefully controlled' patients is a red herring. Tumour cells 'sterilised' by irradiation are, so far, an unsubstantiated fantasy for most of the irradiated patients. Moreover, ophthalmic pathologists are familiar with the fact that mitotic figures are also difficult to find in most non-irradiated melanomas. The 'information (which) has already been given by Char[5] on destruction by radiation of the tumour's integrity' is hypothetical, as appears from the only published mean 10-year follow-up report by Gass[6] (next paragraph).

Paragraph 6 (Concerning...): More favourable results of radiotherapy as compared with enucleation, concerning metastatic death, have never been reported by any author who has presented a >5-year follow-up survival statistic of *all* irradiated patients. Again Oosterhuis *et al.* neglected to substantiate this crucial remark. Gass[6] provided a mean 10-year follow-up survival rate for *all* 27 enucleated and 21 irradiated patients and revealed a 22% death rate after enucleation against 57% after irradiation, while the mean survival after enucleation was >10 years against 3·8 years after irradiation. These figures have not reached statistical significance as yet because of the small numbers of these patients; they are, however, highly impressive for the unbiased reader.

Paragraphs 7-9 with reference to reports of Lommatzsch and Gragoudas. We have not 'failed to mention results of several other long-term studies with a follow-up period of more than four years...' as Oosterhuis *et al.* state incorrectly. We have studied carefully the published reports, which were included in the bibliography. The papers by Augsburger *et al.*[7] Lommatzsch,[8] and Gragoudas *et al.*[9] were published after our paper had been submitted. They cannot, therefore, be used in criticism of our paper. It is of interest that two of these papers present once again statistics on selected groups of patients instead of irradiated patients in toto. The third paper is based on a mean follow-up of 5·4 years. The readers will have noticed that our paper emphasises that after a 5-year follow-up some indications might be provided, but that 10-year or longer follow-up periods are needed to achieve decisive arguments. We have also stressed that tumour-related death after enucleation has appeared to decrease steadily to a low percentage in the second 5-year follow-up period. Tumour biology suggests, however, that after irradiation the remaining tumour tissue will either continue or restart its exponential growth. Then dissemination and death from metastases will tend to increase exponentially in the second 5-year follow-up period, as was shown by Gass.

Irradiation of uveal melanomas is still based on hypotheses and on too short follow-up periods in selected subgroups of patients, by which considerable selection artefacts have been incurred. Patients with uveal melanoma have the right to be treated by enucleation, which eliminates any further dissemination. Radiotherapy of uveal melanomas is justified only in patients with a short life expectancy and in patients who refuse enucleation.

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References

1 Davidorf FA, Lang JR. The natural history of malignant melanoma of the choroid: small vs large tumors. *Ophthalmology* 1975; **79:** 310–20.
2 Thomas JV, Green R, Maumenee AE. Small choroidal melanomas. A long-term follow-up study. *Arch Ophthalmol* 1979; **97:** 861–4.
3 Barr CC, Sipperley JO, Nicholson DH. Small melanomas of the choroid. *Arch Ophthalmol* 1978; **96:** 1580–2.
4 Crawford JB, Char DH. Histopathology of uveal melanomas treated with charged particle radiation. *Ophthalmology* 1987; **94:** 639–43.
5 Char DH. Therapeutic options in uveal melanoma. *Am J Ophthalmol* 1985; **99:** 616–7.
6 Gass JDM. Comparison of prognosis after enucleation vs cobalt-60 irradiation of melanomas. *Arch Ophthalmol* 1985; **103:** 916–23.
7 Augsburger JJ, Gamel JW, Sardi VF, Greenberg RA, Shields JA, Brady LW. Enucleation vs cobalt plaque radiotherapy for malignant melanomas of the choroid and ciliary body. *Arch Ophthalmol* 1986; **104:** 655–61.
8 Lommatzsch PK. Results after β-irradiation (106-Ru/106-Rh) of choroidal melanomas: 20 years' experience. *Br J Ophthalmol* 1986; **70:** 844–51.
9 Gragoudas ES, Seddon JM, Egan K, *et al.* Long-term results of proton beam irradiated uveal melanomas. *Ophthalmology* 1987; **94:** 349–53.

Obituary

R B Harcourt, MA, MB, BChir, FRCS, DO

Mr Richard Brian Harcourt, consultant ophthalmic surgeon to the General Infirmary at Leeds, honorary senior clinical lecturer to Leeds University, and President of the Ophthalmological Society of the United Kingdom, died on 3 November 1987 aged 53.

Brian was born on 3 March 1934, the son of an engineer and the grandson of a surgeon, and was educated at Quarry Bank School, Liverpool, before studying medicine at Trinity College, Cambridge, and St Bartholomew's Hospital, London. After national service in the Royal Air Force he chose ophthalmology as his specialty and undertook his training at the High Holborn branch of Moorfields Eye Hospital. Early in his ophthalmic career he showed a flair for paediatrics, and after spending a year as a Research Fellow in paediatric ophthalmology at the Hospital for Sick Children, Great Ormond Street, and the Institute of Ophthalmology he was appointed to the consultant staff of the General Infirmary at Leeds in 1968. He was made an honorary clinical lecturer to Leeds University and was promoted to honorary senior clinical lecturer in 1978.

At Leeds he developed his expertise in paediatric ophthalmology and in strabismus, so that in a very few years he had become one of the acknowledged experts in these fields. His many publications culminated in the book *The Diagnosis and Management of Ocular Motility Disorders*, written in collaboration with Miss Joyce Mein and published in 1986.

In addition to his extensive clinical practice, he was very active in national and international ophthalmic committees. He was elected a member of council of the Faculty of Ophthalmologists in 1970 and had been its honorary treasurer since 1979. He was a member of the General Optical Council, one of the British representatives on the Section of Ophthalmology of the European Union of Medical Specialists, and represented British ophthalmologists on the board of governors of Moorfields Eye Hospital. In addition to being a member of its court of examiners he had recently been appointed regional adviser in ophthalmology to the Royal College of Surgeons of England. In 1987 he was elected President of the Ophthalmological Society of the United Kingdom, an honour which he particularly appreciated, and he was looking forward with great pleasure to presiding over the annual congress of the society in Harrogate in April 1988.

In recent years he played a major part in developing the interests of ophthamology, not least in his support for the proposed college of ophthalmologists, and was a wise and sympathetic adviser to his colleagues. He always displayed great charm and had an astute and inquiring mind.

In addition to his medical interests Brian Harcourt was a magistrate and a keen gardener, ornithologist, and sailor. He recently obtained his navigator's certificate and had great pleasure in taking his family sailing during his last summer. Above all he was devoted to his family, who were most loving and supportive during his illness.

Brian will always be remembered as a dear friend and colleague, and his death at the height of his career will be a great loss to British ophthalmology.

He leaves a widow, Margaret, and two sons, one a medical student, and a daughter who is training to be an ophthalmologist. BJ

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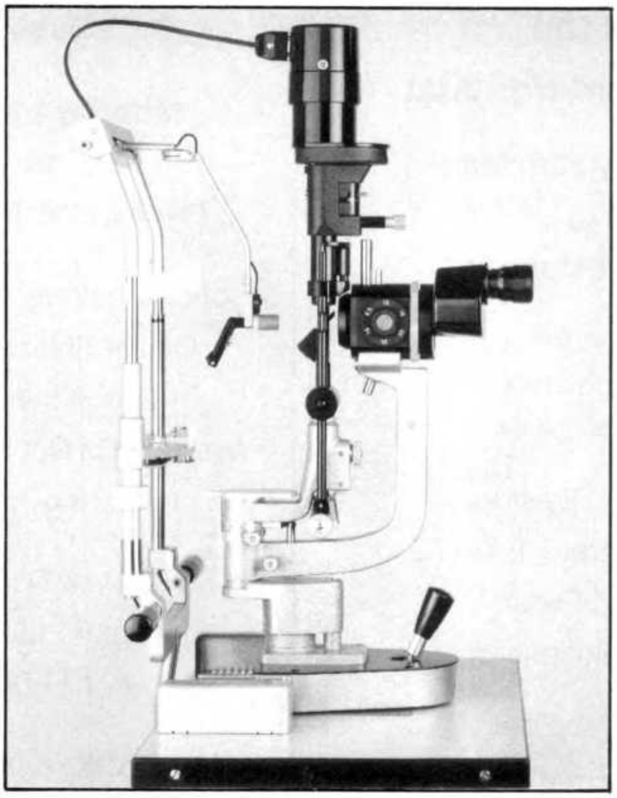

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10.45	Dr Guy Woodgush	Investigation of molecular biology of retinitis pigmentosa
11.00	Professor H. Ikeda	Electrophysiological investigation in inflammatory eye disease
11.15	Dr C. J. K. Ellis	Evidence for dopamine deficiency in Parkinson's disease
11.30	Dr. H. G. Jenkins	Optic neuritis and protein transport of optic nerve
11.45	Dr. J. Robbins	Benzodiazepines and the retina
12.00	Dr Elizabeth Graham	Immunopathogenesis of retinal vasculitis I
12.15	Dr E. Kasp	Immunopathogenesis of retinal vasculitis II
12.30	Dr R. Ross Russell	Retinopathy of carotid disease
12.45–2.00		**Lunch, Demonstrations, Trade Stands**

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2.00	Mr John Brazier	Pupillary function in ocular hypertension and glaucoma
2.15	Dr Mary Gibbens	Consensual ophthalmotonic reaction
2.30	Dr Veronica Ambrose	Fluorophotometry in the assessment of cataract surgery
2.45	Dr I. Fearnley	Fluorophotometry in acute anterior uveitis
3.00	Dr G. James	Ocular sarcoidosis
3.15	Mr Peter Bacon	Is Adie's syndrome a systemic disease?
3.30	Dr Shirley Smith	Screening for complications of diabetes
3.45	Mr Tim ffytche	Iris changes in leprosy
4.00	Mr M. Kerr-Muir	Comparison of post-polymorphous dystrophy and the ICE syndrome
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ASTM CODEN BJOPAL 72 (4) 241–320 (1988)

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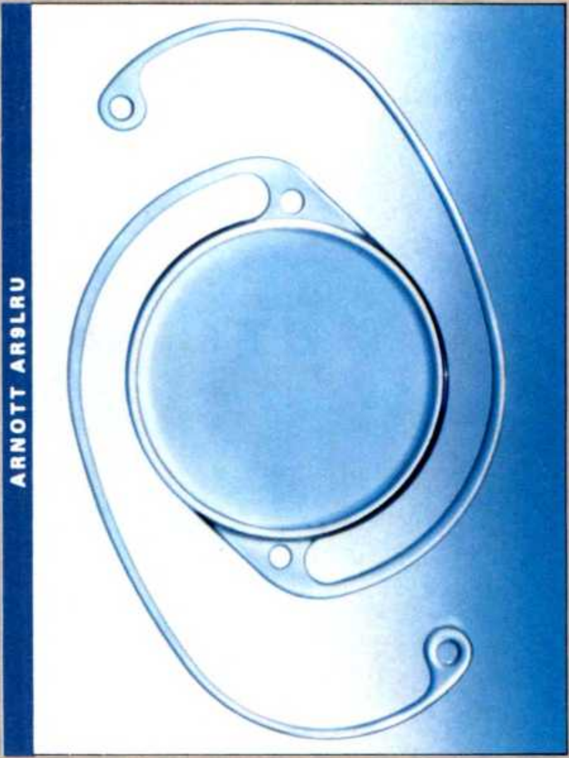

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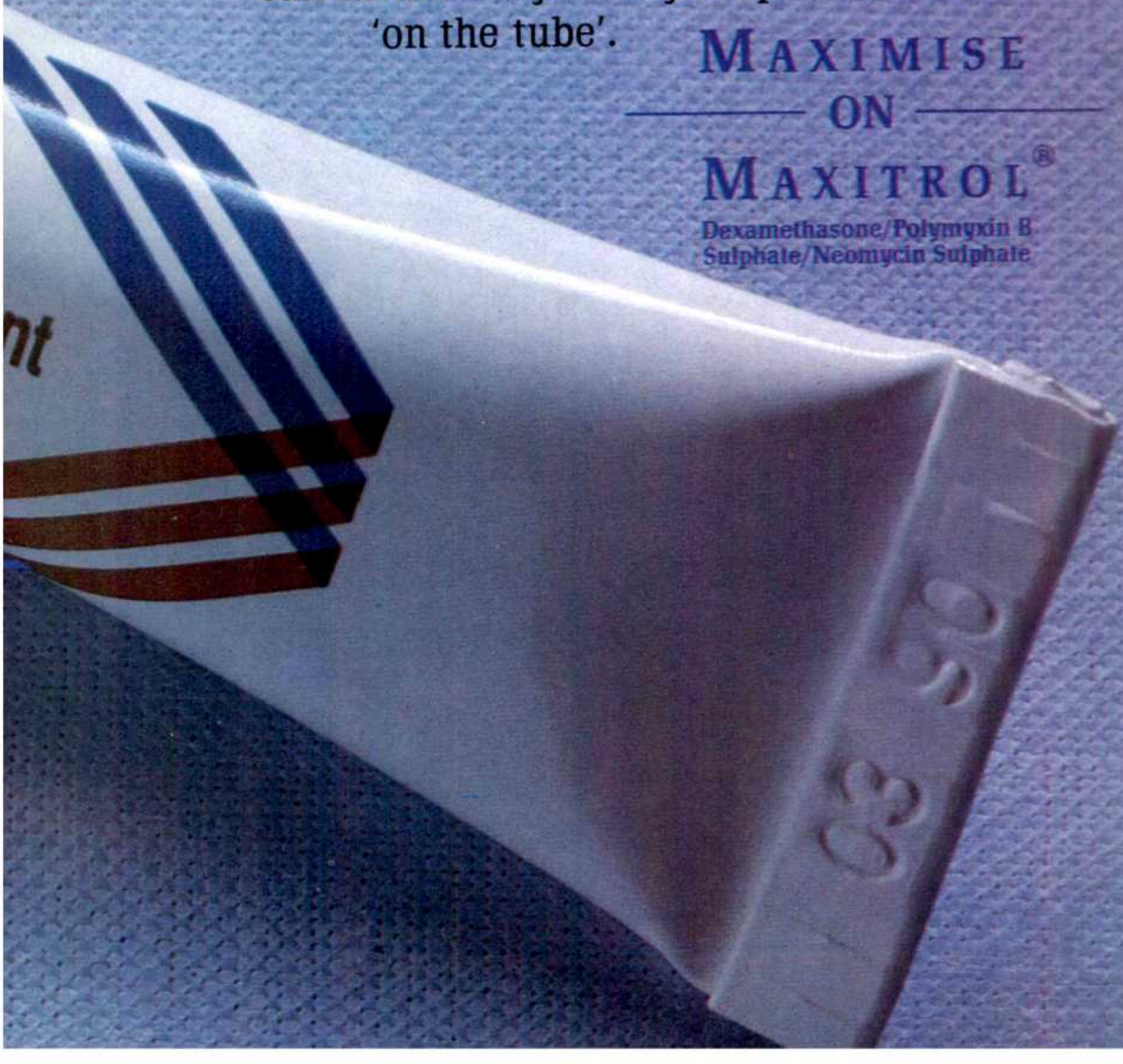

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British Journal of Ophthalmology, 1988, 72, 321

Editorial: Surgical failure after gas injection

The article by Johnston, Maguire, and Logan, in this month's issue, raises some interesting questions.

The vitreal cavity no longer enjoys the privacy it had in earlier days as the more advanced techniques of surgery for detachment increasingly include an invasion of the vitreous with gases, fluids, and a variety of instruments. So far as gases are concerned, air with or without supplementary sulphur hexafluoride seems to be most commonly used. Whereas fluids, either balanced salt solution or silicone oil, may be considered largely as 'space fillers' after quantities of subretinal fluid have been removed, gas has a more specific function. It is said to 'tamponade the break,' though I would prefer the term to 'block up the hole.' Of course it is not really the gas that blocks up the hole; it is the surface-tension-generated skin around the bubble, which I suppose comes to more or less the same thing.

On reading the aforementioned article I was rather uneasy about the explanation of the observed phenomenon: the apparent disturbance of previously flat holes elsewhere or, worse still, the production of holes in previously imperforate lattice elsewhere by means of a gas bubble to a superior position in the vitreal cavity. Consider case 1: a man had a superior detachment with a U tear but also three other tears in flat retina below. After drainage, 1 ml of SF6 gas was injected into the vitreous cavity. Later the three inferior tears came off, and it is recorded that 'the intravitreal gas bubble opened the inferior tears widely by increasing vitreoretinal traction when the patient was erect.'

This conclusion needs fairly careful consideration. One might start by running through the sequence of events. Here was an eye with a superior detachment and subretinal fluid. The subretinal fluid was removed and the eye presumably collapsed to suit. Ocular volume was restored by an injection of gas 'into the vitreous body' *before* scleral buckling.

If we assume that vitreoretinal bands were present, it is fair to say that directly or indirectly various parts of the retina would tend to be connected with one another via the bands. Thus, if initially (when the detachment occurred) a horseshoe tear is 'pulled down' by the vitreous and its bands, it stands to reason that if it is pushed up again with an air bubble the same bands will exert traction on the lower retina. In other words, it is not the air bubble that pulls the lower retina off: it is the upper retina that pulls it off via the vitreoretinal bands. It follows from this that if a large enough buckle is put in *before* the air injection the phenomenon should not occur, since upward movement of the superior retina at the site of the tear would be minimised.

We may look at it another way and consider the bubble within the vitreous invested in its surface-tension-generated skin. Around the bubble the vitreous fibres are certainly stretched, hence exerting extra tension on the supplementary tears: all the more reason to buckle first.

These may be worrying thoughts but in practice do they really matter? If results such as we are now used to seeing in papers by detachment experts, such as the 96% and 90% rates quoted in two selected references in Johnston, Maguire, and Logan's paper, are typical, then perhaps the problems are more theoretical than practical. However, the authors are certainly to be congratulated for bringing this hazard to our attention and possibly initiating work which might lead to even further refinements in retinal detachment technique.

REDMOND J H SMITH

British Journal of Ophthalmology, 1988, **72,** 322–325

Failed retinal surgery caused by intraocular gas injection

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SUMMARY Four patients developed inferior retinal redetachment following initially successful surgery which included intraocular injection of air and sulphahexafluoride (SF6) mixture. In each case the intravitreal gas bubble produced vitreoretinal traction which opened inferior retinal breaks and led to retinal separation. Cautious use of intraocular gas is advised when bullous upper rhegmatogenous retinal detachments are accompanied by inferior retinal breaks.

The use of intravitreal air injection to achieve internal closure of retinal breaks was advocated by Rosengren in 1938.[1] More recently Norton[2] and Gilbert and McLeod[3] described surgical procedures with air or sulphur hexafluoride (SF_6) that overcome the difficulties presented by bullous rhegmatogenous retinal detachment and fish-mouthing of large equatorial retinal breaks. These techniques have proved reliable. However, our recent experience suggests that in certain cases intraocular gas may reverse initially successful reattachment surgery. We describe four patients who developed inferior retinal redetachment following uneventful retinal surgery which included intraocular injection of gas.

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Case reports

CASE 1

A 71-year-old man developed a deep upper-half retinal detachment in his right eye. One large U-shaped tear was situated at the upper temporal equator, and three small flap tears were found at the inferior temporal quadrant within attached retina (Fig. 1, A). A retinal detachment procedure was performed with a piece of solid silicone (287 tire) explant and encircling 240 band. Before scleral buckling, subretinal fluid was drained and the ocular volume restored with 1 ml SF_6 gas injected into the vitreous cavity. The retinal breaks were surrounded by cryo application. The retina was attached at the

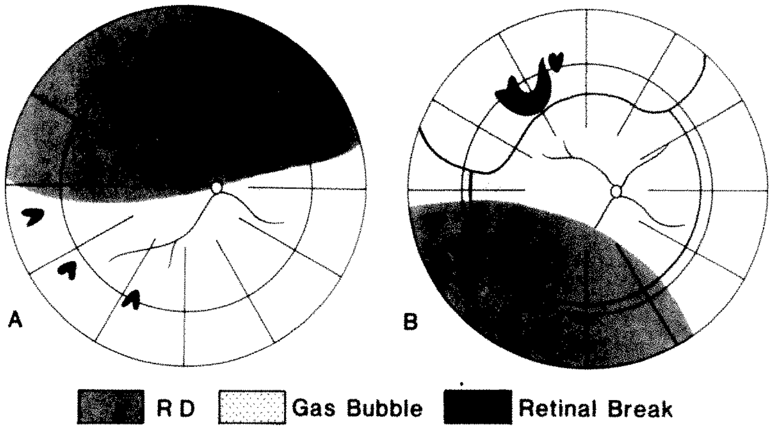

Fig. 1A *Superior bullous retinal detachment. Inferior retina contains three flat tears* (B). *Gas bubble holds the superior retinal break and buckle in apposition, but subretinal fluid has collected below.*

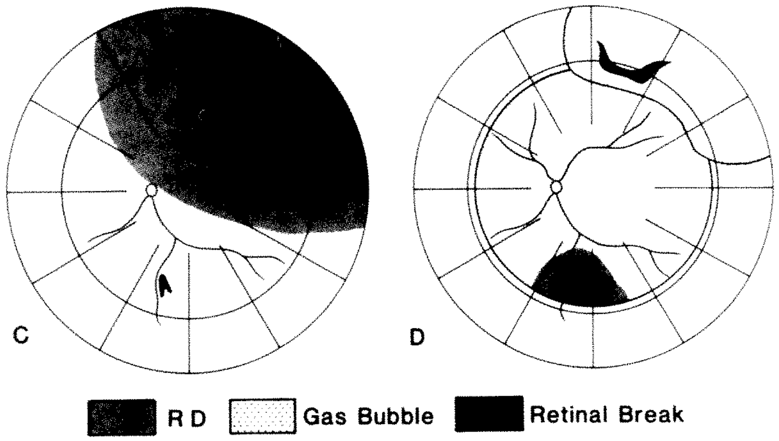

Fig. 2C *Large superior balloon detachment. The inferior retina contains one flat postequatorial tear* (D). *Gas bubble holds the superior break and buckle in apposition, while subretinal fluid collects around the inferior break.*

first postoperative day, but by the second day there was an inferior bullous retinal detachment associated with the three lower tears (Fig. 1, B). The intravitreal gas bubble opened the inferior tears widely by increasing vitreoretinal traction when the patient was erect. The silicone tire was extended circumferentially to cover these tears, and subretinal fluid was released. The retina reattached but three weeks later developed total detachment with widespread changes of proliferative vitreoretinopathy.

CASE 2

A 59-year-old woman was referred with a superior balloon retinal detachment in her left eye. The detached retina contained a large U-shaped tear, and the inferior retina was attached with one post-equatorial flap tear (Fig. 2, C). A retinal detachment procedure was performed with a broad circumferential buckle, encircling band 240, and incomplete drainage of subretinal fluid. Cryotherapy was applied to the retinal breaks, and a scleral buckle was not considered necessary for the inferior break. After the operation there was residual subretinal fluid, and the upper retinal break remained elevated with a typical fish-mouth appearance. Five days later 0·5 ml of pure SF_6 gas was injected into the vitreous cavity, and the following day the superior retina was flattened on the buckle. Three days later subretinal fluid collected round the inferior retinal break, which was held open by transvitreo-retinal traction enhanced by movement of the intravitreal gas bubble (Fig. 2, D). The inferior break was successfully closed with a 7 mm radial sponge.

CASE 3

A 50-year-old woman developed a bullous detachment of the left superior retina which contained two U-shaped tears and three round holes (Fig. 3, E). The lower retina was attached with pre-equatorial lattice degeneration at the inferior periphery. After external drainage of subretinal fluid the retina was repositioned with 2 ml of 20% SF_6 gas and air mixture, which was injected into the vitreous cavity through the pars plana. The retinal breaks were

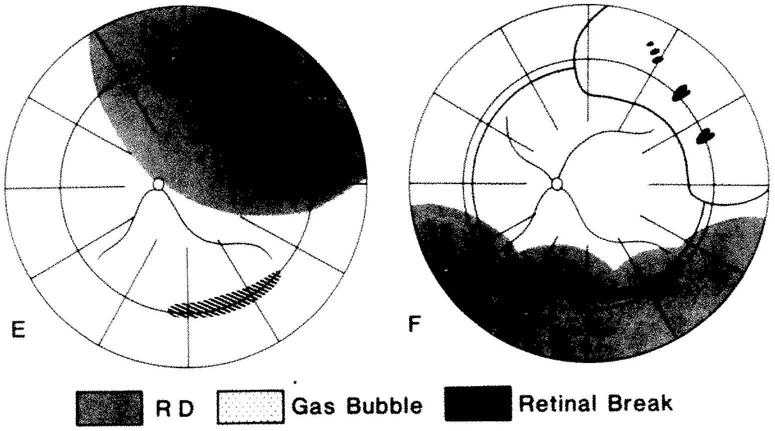

Fig. 3E *Superior balloon detachment. Inferior retina contains visible lattice degeneration* (F). *Gas bubble holds the superior retina and buckle in apposition. Three new tears resulted in inferior retinal detachment.*

treated with cyro application. The retinal breaks were buckled with a piece of solid silicone tire (287) and encircling band 240. On the first postoperative day the retina was attached; on day 2 an inferior bullous retinal detachment developed with no identifiable retinal break. The circumferential buckle was extended to cover the inferior retinal periphery; however, this proved unsuccessful. Examination revealed fresh inferior retinal breaks (Fig. 3, F) which were held open by vitreous traction even though the scleral buckle was substantial. A third surgical procedure consisted of vitrectomy, internal gas/fluid exchange, and argon laser endophotocoagulation, which achieved reattachment of the retina.

CASE 4

A 67-year-old man developed a bullous detachment of the left superior retina which contained two U-shaped tears. After external drainage of subretinal fluid the pars plana was penetrated with a 27 gauge needle and the ocular volume restored with 1·5 ml of 20% SF_6 gas and air mixture, which was injected into the vitreous gel. The retinal breaks were treated by cryo application and supported on a broad buckle and encircling band. On the first postoperative day the retina was reattached. On day 3 the inferior retina was elevated by vitreous traction, which increased when the intraocular gas bubble was displaced superiorly. Examination revealed three small inferior breaks at the posterior vitreous base. The retina attached after a second surgical procedure which comprised vitrectomy and rebuckling.

Discussion

Rosengren[1] introduced the method of intravitreal air injection for rhegmatogenous retinal detachment. This has been modified by many surgeons[2-5] to combine scleral buckling, subretinal fluid drainage, and intravitreal air or SF_6 gas injection for difficult cases such as bullous retinal detachments with large equatorial breaks. Stanford and Chignell[6] reported an unacceptable incidence of failure of these cases where a technique of non-drainage or drainage without intravitreal gas injection is used. The deeply separated retina prevents accurate localisation and controlled cryotherapy of the retinal breaks. When subretinal fluid is drained, the retina settles on the buckle in folds, which creates the classical fish-mouth appearance. Many of these difficulties are avoided by preoperative reduction in the height of retinal detachment by means of an inferior rectus fixation suture.[7] When immobilisation of the globe does not produce settling of the retinal balloon, a technique of subretinal fluid drainage, intravitreal air injection, cryopexy, and episcleral explant (D-ACE)[3] is employed. Using this technique for bullous retinal detachment Stanford and Chignell[6] and Gilbert and McLeod[3] reported surgical success rates of 96% and 90% respectively. However, our four patients developed retinal redetachment, which we believe was related to the presence of intraocular gas. Two patients had pre-existing inferior retinal breaks within attached retina, and one had widespread lattice degeneration of the lower retina. All four patients developed opening of inferior retinal breaks and retinal separation following the use of intraocular gas, and in two cases fresh breaks were

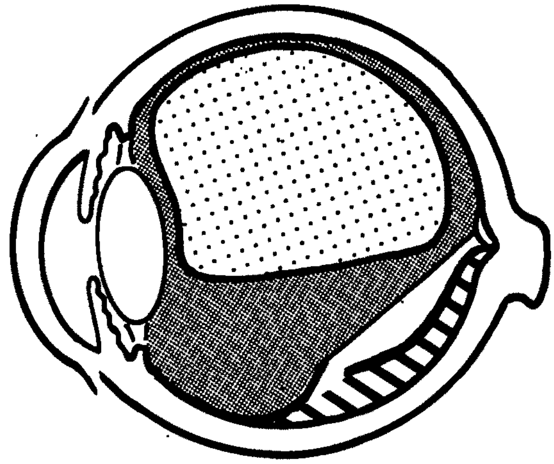

Fig. 4 *Superior intragel gas bubble produces vitreous traction on inferior retinal break by stretching the posterior hyaloid.*

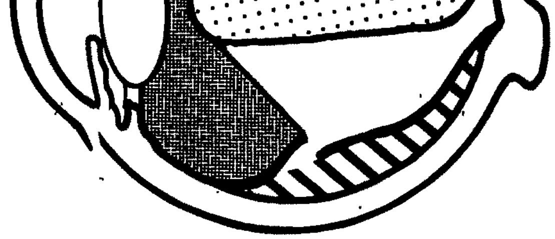

Fig. 5 *Superior displacement of gas bubble into the retrohyaloid space creates inferior vitreous traction on the retinal break by anterior movement of the posterior hyaloid.*

detected following the first operation. Three patients were successfully treated by reoperation consisting of vitrectomy and intravitreal gas tamponade in two cases and rebuckling in the other. One patient developed proliferative vitreoretinopathy after a second rebuckling procedure, and further surgery was refused.

Gilbert and McLeod[3] and Stanford and Chignell[6] both report that intraocular gas injection has few serious complications, which mostly comprise subretinal haemorrhage at the subretinal fluid drainage site. However, Dreyer[8] has described a patient who developed fresh inferior retinal breaks following retinal surgery which included intraocular injection of pure SF_6 gas. Our four patients are comparable to Dreyer's case, and we suggest that superior displacement of the intraocular gas bubble caused increased vitreoretinal traction at the site of inferior retinal breaks and vitreous base. The proposed mechanism is due to stretching of the posterior hyaloid by the superiorly positioned gas bubble and can occur where the gas bubble is within the vitreous gel (Fig. 4) or has migrated into the retrohyaloid space (Fig. 5).

We agree that the D-ACE technique is valuable for difficult bullous detachments. However, caution should be exercised in the presence of preoperative inferior retinal breaks or lattice degeneration. Internal gas tamponade is necessary only for a short postoperative period to close superior retina breaks. When inferior retinal breaks exist prior to surgery, we believe it is advisable to use air rather than SF_6 gas for internal tamponade of superior breaks. The delayed absorption and postoperative expansion[2] of SF_6 gas may increase and prolong vitreoretinal traction, which opens or creates inferior retinal breaks.

References

1 Rosengren B. Cases of retinal detachment treated with diathermy and injection of air into the vitreous body. *Acta Ophthalmol (Kbh)* 1938; 16: 573–9.
2 Norton EWD. Intraocular gas in the management of selected retinal detachments. *Ophthalmology* 1973; 77: 85–98.
3 Gilbert C, McLeod D. D-ACE surgical sequence for selected bullous retinal detachments. *Br J Ophthalmol* 1985; 69: 733–6.
4 Chawla HB, Colciro JA. Retinal detachment treated with intravitreal air: an evaluation of 241 cases. *Br J Ophthalmol* 1977; 61: 588–92.
5 McLean EB, Norton EWD. Use of intraocular air and sulfur hexafluoride gas in the repair of selected retinal detachments. *Mod Probl Ophthalmol* 1974; 12: 428–31.
6 Stanford MR, Chignell AH. Surgical treatment of superior bullous rhegmatogenous retinal detachments. *Br J Ophthalmol* 1985; 69: 729–32.
7 Johnston PB, Maguire CJE, Logan WC. Management of superior half bullous retinal detachment. *Br J Ophthalmol* 1981; 65: 618–22.
8 Dreyer RF. Sequential retinal tears attributed to intraocular gas. *Am J Ophthalmol* 1986; 102: 276–8.

Accepted for publication 5 March 1987.

British Journal of Ophthalmology, 1988, **72**, 326–337

Fluorescein angiography of anterior uveal melanocytic tumours

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SUMMARY A retrospective analysis of 32 cases of anterior uveal melanocytic tumours included 14 cases in which the tumours could be categorised histologically as malignant, of intermediate cytology with equivocal features of malignancy, or as benign progressive naevi. An additional eight cases without a histological diagnosis were included as benign naevi, because there had been no change in their clinical characteristics after a minimum follow-up of four years. Clinical features and iris fluorescein angiographic (IFA) findings were analysed with respect to these groups in an attempt to identify features predictive of malignant or locally invasive behaviour. Very small tumours were more likely to be benign ($p=0.029$). Glaucoma and episcleral vascular dilatation occurred in ciliary body tumours only. Tumours involving the anterior chamber angle proved more likely to be malignant ($p=0.019$). IFA showed a disorganised vasculature and gross late leakage in 4/7 (56%) malignant melanomas as well as in 2/6 (33%) tumours with intermediate cytology. No benign tumours showed these features. Four out of nine (44%) benign tumours, but no tumours with malignant or intermediate cytology, showed complete masking of fluorescence. Early leakage of dye from tumour vessels and a geometric tumour vasculature were not specific features of any tumour category. IFA correlated with the cytology and behaviour of anterior uveal melanocytic tumours in 11/22 (50%) of our cases.

Melanocytic tumours are the commonest that affect the iris. They may behave in three ways. Most are slow growing or static. Some are locally invasive, with benign cytological characteristics, and may be regarded as benign progressive naevi even though local growth may result in the loss of the eye.[1] Lastly they may metastasise, though this is rare, occurring in 3–5% of cases.[1,2] Ciliary body lesions encroaching on the iris have a worse prognosis and are sometimes impossible to differentiate clinically from a primary iris tumour. Clinical features apart from rapid growth are of little value in predicting the behaviour or cytological characteristics of a lesion.[1,3] Excision biopsy carries appreciable morbidity in eyes which are generally asymptomatic with good sight.[1] A non-invasive investigation that might predict tumour behaviour and cytology would assist in the management of these lesions.

It has been suggested that iris fluorescein angiography (IFA) is capable of differentiating between tumours with and without metastatic potential.[3,4] Fluorescein angiography allows assessment of the degree of abnormality of the iris tumour vasculature as well as secondary effects of tumour growth on surrounding tissues. It is assumed that abnormal patterns of tumour vasculature and permeability of iris tumour vessels reflect the degree of differentiation and cytological abnormality of the tissues. The pathophysiological associations of these angiographic features have been discussed elsewhere.[3,4]

There has been general agreement in the previous literature on the interpretation of certain patterns of IFA in iris melanocytic tumours. Masking of fluorescence by the lesion has been considered by all authors who have described it as indicative of a benign lesion.[3-7] The presence of a geometric, organised (leaf-like,[6] network,[3] filigree[4]) vascular pattern has been associated with benign lesions by some[4,6] and by others as potentially malignant.[3] Disorganised irregular tumour vasculature has similarly been considered to denote malignancy.[4,5] The importance of leakage into and around the tumour is open to dispute. Some have regarded it as indicative of

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malignancy,[7] especially if early or profuse,[3,4,6] but most have considered it associated with both benign and malignant tumours.[3-5] Areas of leakage at sites remote from the tumour such as the pupil margin are probably of no significance.[3,4]

Unfortunately most of the earlier reports are difficult to evaluate because of doubt about the histopathological criteria for a diagnosis of malignancy.[1] Recently Jakobiec *et al.*[4] evaluated the cytological characteristics and described the fluorescein appearance of a series of iris melanocytic tumours, but, as they included only two cases that were considered to be malignant, reservations have to be made about their interpretation of IFA patterns. Tumours of uncertain or intermediate characteristics have been difficult to categorise by any system of fluorescein or pathological classification, further complicating the analysis of data in previous studies.

In the past 10 years we have encountered 32 cases of melanocytic iris tumour, 14 of which have been excised and evaluated histologically with reference to the nine group classification of Jakobiec and Silbert.[1] A simple method for describing IFA patterns was used and the fluorescein characteristics correlated with the histopathological classification and behavioural characteristics of the tumours. These results were analysed to determine which fluorescein parameters were most helpful in indicating the likely cytological composition of the tumours and their future behaviour.

Patients and methods

Thirty-two cases were initially referred to one of us (RJM) for clinical evaluation and IFA. Twenty-one cases have been reviewed in the last year: 11 cases have been reviewed with repeat photography and angiography, 10 have been followed up by a review of the case notes supplied by the referring practitioner, and three have died. Eight cases were lost to follow-up.

Examination. Each patient had a full ophthalmological examination with slit-lamp microscopy, gonioscopy, applanation tonometry, and funduscopy. IFA was performed with a Zeiss motorised slit-lamp camera with an accessory halogen illuminator and a 16 mm cine camera as previously described.[8] Photographs were taken 7 seconds after injection of 5 ml of 20% fluorescein and repeated every 1·5 seconds with late pictures at 3 minutes.

Interpretation of iris angiograms. The IFAs were reviewed in each case and classified by a simple system in which each of four possible tumour angiographic features was assessed and graded separately. These were the degree of masking, the timing and degree of any leakage from the tumour vessels, the structure of the tumour vasculature, and the phase of filling of the tumour vessels.

Pathology. Excision biopsies were all examined by one of us (AG) using light microscopy and, in selected cases, electron microscopy. The tumours were classified according to the nine group classification of Jakobiec and Silbert[1] (J&S 1–9). For simplicity the classification was reduced to three groups: malignant melanomas (J&S 7, 8, 9), intermediate melanocytic tumours (J&S 5, 6), and benign or progressive naevi (J&S 1, 2, 3, 4). Lesions included in the intermediate group presented cytological features which did not allow clear categorisation as benign or malignant. It encompassed tumours that could be classified histologically as spindle cell naevus with surface plaque (J&S 5) and borderline spindle cell naevus (J&S 6). Unlike Jakobiec and Silbert,[1] we considered that these cytological features

Table 1 *Classification of anterior uveal tumours*

Groups and definitions	*Number in group*	*Classification**	*Number in class*
Maligant melanomas (unequivocal cytological signs of malignancy including Jakobiec and Silbert groups 7–9)	7	Epithelioid cell melanoma	1
		Mixed spindle and epithelioid cell melanoma	1
		Mixed spindle cell and epithelioid cell melanoma (ciliary body)	3
		Spindle cell melanoma	2
Intermediate melanocytic tumours (equivocal cytological features not permitting clear categorisation as benign or malignant including Jakobiec and Silbert groups 5 & 6)	6	Borderline spindle cell naevus	4
		Spindle cell naevus with surface plaque	2
Benign or progressive naevi (benign cytological characteristics including Jakobiec and Silbert groups 1–4) or no change in clinical characteristics after minimum follow-up of 4 years	9	Intrastromal spindle cell naevus	1
		No change in clinical characteristics after minimum follow-up period of 4 years	8
Unknown group (less than 4 years' follow-up or no histology available)	10		

*The histological classification followed that of Jakobiec and Silbert. All histological diagnoses were for primary iris tumours except for the three ciliary body tumours involving iris.

Table 2 *Age and sex distribution and follow-up period and deaths in patients with anterior uveal tumours*

	Tumour group					*Total*
	Malignant iris	*Malignant ciliary body*	*Intermediate*	*Benign*	*Unknown*	
Age: Mean	35	48	47	70	51	53
Range	25–46	43–54	27–59	56–81	22–84	22–84
SD	8·6	5·5	10·9	8·5		
Sex: M/F ratio	4:0	1:2	4:2	3:6	7:4	19:13
Follow-up period in months:						
Mean	65	25	27	80	16	43
Range	1–97	14·5–51	6–67	51–144	1–60	1–144

ANOVA on age distribution in malignant, intermediate, and benign tumour groups. F statistic 16·89; p=<0·001.

could not be regarded as unequivocal evidence of benignity. Three ciliary body tumours have been included as these presented clinically as peripheral iris tumours.

The remaining tumours without histology were each allocated to one of two groups on the basis of their clinical and behavioural characteristics—benign naevus or unknown. The benign naevus group included lesions that had been observed for a minimum of four years without change. The unknown group included all the remaining tumours in which there was either no histological diagnosis, evidence of changing clinical characteristics, or a follow-up period of less than four years.

Statistical methods. Analysis of variance (ANOVA) was used to analyse the differences in the age distribution of subjects in the different tumour groups and the χ^2 test to analyse the proportional data when appropriate.

Results

Table 1 shows the distribution of tumours into the four groups: malignant melanomas (malignant group), intermediate melanocytic tumours (intermediate group), benign or progressive naevi (benign group), and unknown. The age and sex characteristics and the follow up periods are shown in Table 2. ANOVA shows that there are significant differences in the age distribution for the different tumour groups (p=<0·001). Table 3 shows the length of history together with the number of patients in each group in whom the tumour was discovered at an ophthalmic examination for refraction or symptoms unrelated to the tumour. It can be seen that neither the length of history nor the discovery of an asymptomatic tumour on routine examination is related to the eventual outcome. Table 3 also shows the surgical management and deaths. Of the three patients who died one had a malignant ciliary body tumour and had a presumptive diagnosis of metastatic disease related to this. Unfortunately no post-mortem examination was carried out to confirm the cause of death. Of the remaining two, both in the unknown group, one died of metastatic disease for which no primary tumour was identified and once again no

Table 3 *History*

	Tumour group					*Total*
	Malignant iris	*Malignant ciliary body*	*Intermediate*	*Benign*	*Unknown*	
Length of < 1			3		1	4
history 1–2		2	1	1	2	6
in years 3–4		1		2		3
5–10	3		1	4	2	10
10–20				3	2	5
>20			1	1		2
Life	1			1		2
Discovered on routine examination	1	1	3	8	5	18
Surgical management						
Iridectomy	3		5	1		9
Iridocyclectomy	1		1			2
Enucleation		3				
Deaths		1 Metastatic			1 Metastatic (primary uncertain) 1 Heart dis.	

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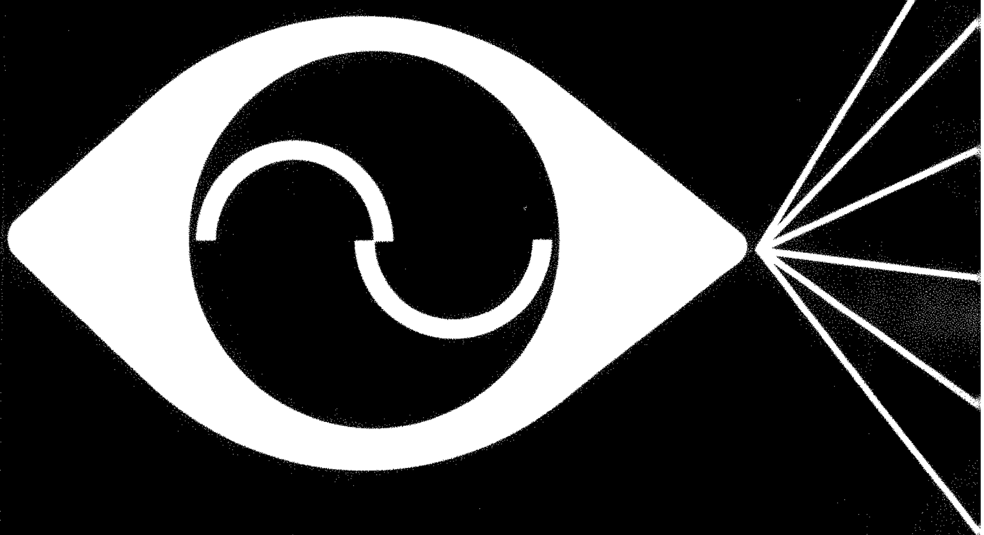

Topical beta-blocker for the management of glaucoma

DISPERSA

Teoptic: Abbreviated prescribing information
Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% Eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity. **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

Offers protection of visual function

Significant reduction in IOP levels

Well tolerated locally and systemically

Content of benzalkonium chloride only 0.005%

pH value 6·7

Five good reasons for prescribing Teoptic

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic NHS Cost and Product Licence Numbers:** Teoptic 1% Eye-Drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% Eye-Drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP. Further information is available on request to the above address.

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Table 4 *Clinical features in relation to tumour classification*

Clinical Features	*Tumour group*				
	Malignant iris (n=4)	*Malignant ciliary body (n=3)*	*Intermediate (n=6)*	*Benign (n=9)*	*Unknown (n=10)*
Peripheral*	2	3	4	3	3
Sector*	1	–	2	2	3
Other	1	–	–	4	4
Size* (area)					
<¼ quadrant	0	0	0	4	1
¼–1 quadrant	4	3	6	5	9
Growth	2	1	1	2	–
Glaucoma	–	3	1	–	–
Ring tumour	1	–	–	–	–
Episcleral vascular dilatation	–	3	–	–	–
Sectoral cataract	–	1	–	–	–
Satellite lesions	1	1	–	–	–
Uveitis	1	–	1	–	–
Hyphaema	–	–	1	–	–
In angle*	3	3	3	1	2
Cystic	1	–	1	–	4
Touching cornea	1	1	2	1	2
Non-pigmented	2	–	2	1	3
Distorted pupil	2	1	3	3	4
Ectropion uveae	2	–	3	2	3
Tumour vascularity	2	1	4	2	2

*The frequency of these features was tested by the χ^2 test in the malignant, intermediate, and benign groups.

The only significant values at the 5% level were for tumours of less than ¼ quadrant in area, which occurred only in the benign group (p=0·029), and the presence of tumour in the angle (p=0·019), which was more frequent in the malignant and intermediate groups.

post-mortem study was performed. The remaining death was from unrelated cardiac disease. The incidence of prominent clinical features in each group is shown in Table 4. In this series growth was recorded in all tumour categories, including tumours of two patients in the benign group who reported slow growth over many years that did not continue during the follow up period of 5–7 years. Glaucoma and episcleral vascular dilatation were features of ciliary body tumours but were not identified in the iris tumours in this series. Some of these clinical features were sufficiently common to allow statistical analysis by the χ^2 test to compare their frequency in the different groups; these are asterisked in Table 4. Because none of the tumours in this series exceeded one quadrant in area, the effect of size was difficult to quantify, though very small tumours, involving less than 1 quarter of a quadrant, were more likely to be benign than larger tumours (p=0·029). Moreover tumours involving the angle were more often malignant than benign (p=0·019). As tumours of all sizes involved the angle, this finding is probably independent of size, but numbers were not large enough for statistical analysis. Except for these findings the different behavioural and histopathological groups could not be distinguished on the basis of clinical features.

The IFA characteristics and their occurrence in the different tumour groups are shown in Table 5. Five of these characteristics were selected for correlation with the three tumour groups composed of the 22 cases for which the tumour cytology and behaviour were known. They were disorganised vascular pattern, early leakage, a gross late degree of leakage, complete masking ('angiographic silence'), and geometric vascular pattern. These findings are summarised in Table 6, which shows that disorganised vascular pattern and gross late leakage did not occur in the benign group at all. However, they were not common in either the malignant or intermediate group: disorganised vascular pattern occurring in only 4/7 (57%) of the malignant tumours (Figs. 1A–C), and in 2/6 (33%) of the intermediate group (Figs. 2A–C), while early leakage was found in only 2/7 (29%) of malignant tumours (Figs. 3A–E), 2/6 intermediate group tumours (Figs. 4A–C) and 1/9 tumours in the benign group (Figs. 5A, B). One or more of these three IFA characteristics were present in 6/7 (86%) of malignant tumours. The same was true of 3/6 (50%) of the intermediate group and one case in the benign category, a tumour that had been followed up without change for eight years. Early leakage was not specific for tumours of malignant or intermediate cytology. Gross late leakage was uncommon.

Complete masking was only found in 4/9 (44%) of the benign group (Figs. 6A, B). Geometric vascular pattern occurred in all groups (Figs. 5, 7A–E, 8A, B)

Table 5 *Classification system for IFAs and number of tumours in each IFA class*

Fluorescein characteristic Each assessed and graded separately	*Tumour group*				
	Malignant iris	*Malignant ciliary body*	*Intermediate*	*Benign*	*Unknown*
Masking:					
Complete	–	–	–	4	3
Incomplete	3	3	2	5	–
None	–	–	4	–	–
Leakage:					
None	–	–	–	–	–
Early moderate*	1	1	2	1	1
Early gross	–	–	–	–	–
Late moderate†	3	1	5	4	7
Late gross‡	–	–	1	–	–
Filling pattern:					
Geometric with vessels of similar calibre	2	–	4	3	5
Disorganised with vessels of varying calibre	2	2	2	–	–
Dilated radial vessels	–	2	1	–	2
Phase of tumour filling:					
In phase with iris	3	2	5	1	5
Out of phase with iris	1	1	1	2	1
Different phases within tumour	–	–	–	–	–
Patients having repeat angiography	2	1	1	5	2

*Early, within 10 seconds of appearance of dye in tumour. †Late, 10 seconds or more after appearance of dye in tumour. ‡Dye obscuring all detail of tumour.

except the malignant ciliary body melanomas and consequently appears to be non-specific for tumour cytology or behaviour.

The χ^2 test was used to compare the frequency of each feature in the different tumour groups. No significant difference could be identified between intermediate melanocytic tumours and either benign naevi or malignant melanomas for any individual fluorescein characteristic, though the presence of a disorganised vascular pattern did not occur in the benign group ($p=0{\cdot}055$). A higher proportion of tumours in the malignant and intermediate groups compared with the benign group showed one or more of the characteristics that others have previously regarded as being indicators of malignancy ($p=0{\cdot}019$).

Table 6 *Analysis of fluorescein characteristics expected to be specific indicators of tumour cytology and behaviour*

Fluorescein characteristics	*Tumour group*			
	Malignant iris Malignant ciliary body *n=7*	*Intermediate* *n=6*	*Benign* *n=9*	χ^2 *test*
Fluorescein characteristics indicative of malignant melanomas				
Disorganised vascular pattern	4 (57%)	2 (33%)	–	$\chi^2=5{\cdot}170$ $p=0{\cdot}055$
Early leakage	2 (29%)	2 (33%)	1 (11%)	$\chi^2=1{\cdot}353$ $p=0{\cdot}508$
Gross late leakage	–	1 (17%)	–	$\chi^2=1{\cdot}419$ $p=0{\cdot}492$
Any of above	6 (86%)	3 (50%)	1 (11%)	$\chi^2=7{\cdot}916$ $p=0{\cdot}019$
Fluorescein characteristics indicative of benign naevus				
Complete masking	–	–	4 (44%)	$\chi^2=5{\cdot}140$ $p=0{\cdot}077$
Geometric vasculature	2 (29%)	4 (66%)	3 (33%)	$\chi^2=5{\cdot}611$ $p=0{\cdot}060$
Any of above	2 (29%)	4 (66%)	7 (78%)	$\chi^2=3{\cdot}650$ $p=0{\cdot}161$

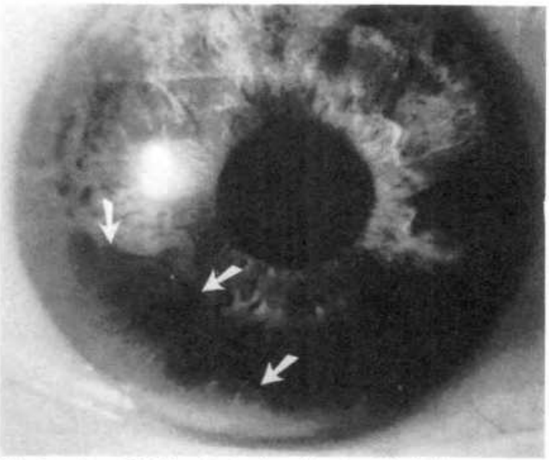

Fig. 1 *Case 17. Mixed spindle cell and epithelioid melanoma (ciliary body). In this and subsequent clinical photographs the arrows point to the tumours.* A: *Clinical appearance of a tumour, involving the angle, that was deeply pigmented and markedly vascular. Associated findings were iris freckles and heterochromia, pigment in the angle, and a distorted pupil.*

Follow-up. Angiography was repeated in 11 cases. No change in the fluorescein characteristics was noted in any case apart from an increase in the size of some lesions (Fig. 7). In three instances when tumours were excised and found to be cytologically malignant there had been evidence of growth on the angiogram. In one case postoperative angiography confirmed the presence of vascularised metastases that had seeded on to the surface of the iris when the tumour fragmented at the time of surgery (Fig. 3).

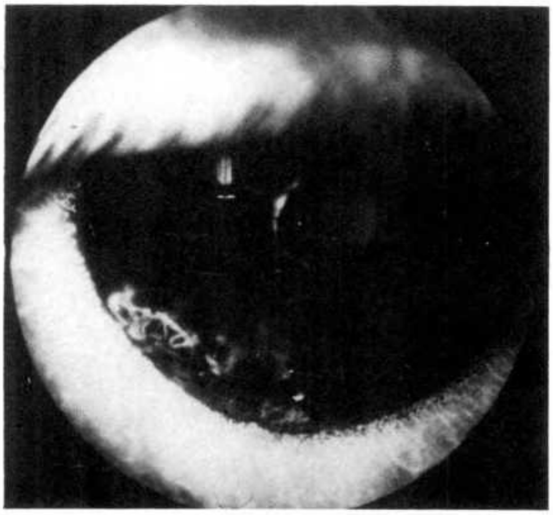

Fig. 1B *IFA showing a disorganised vascular pattern filling out of phase with the iris vessels.*

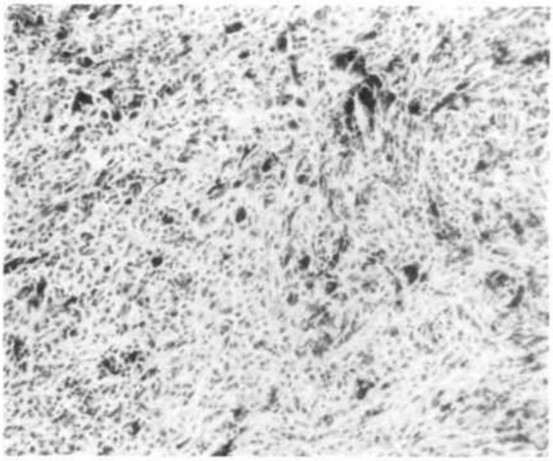

Fig. 1C *The tumour is composed of both spindle and epithelioid cells. H and E, ×115.*

Discussion

There is no reliable clinical method of predicting tumour behaviour apart from observation of rapid growth involving the surrounding tissues or frank metastasis. Cytological features are a recognised way of determining whether a tumour may have the potential to display this behaviour. Unfortunately the criteria are not sufficiently precise or constant to permit unfailing accuracy in the diagnosis of anterior uveal melanocytic tumours.[1 2 9] However, it has been suggested that IFA findings reflect both tumour behaviour and cytology,[3-7] although here again the criteria are open to dispute. Difficulty in the interpretation of fluorescein findings has been complicated for some cases, in which biopsies were undertaken after IFA, by doubt about the basis of the cytological evaluation.[4] This arose because the descriptions of the tumour histology were incomplete. Although the prognostic inferences drawn by Jacobiec and Silbert[1] from their analysis of the histological features of a series of iris melanomas have been criticised,[9] their scheme still provides a good basis for describing the morphology of these tumours. Its chief merit is that it provides sufficient detail for reasonably precise categorisation of individual biopsy specimens. We have used these histological categories in our retrospective analysis of 32 cases of anterior uveal melanocytic tumours which provided 22 cases in which the behaviour and cytology of the lesions could be used to clearly categorise them into three groups—malignant, intermediate, and benign. This has enabled analysis of clinical and fluorescein features to establish whether any of these are reliable predictors of these categories of tumour.

In this series it is interesting that the patients with

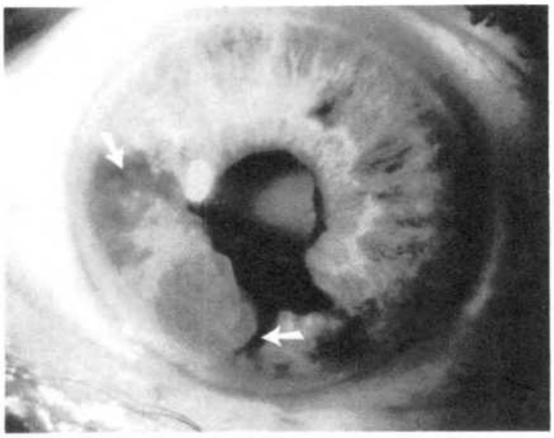

Fig. 2 *Case 11. Spindle cell naevus with surface plaque (iris).* A: *Clinical appearance showing an elevated lesion with marked ectropion uveae.*

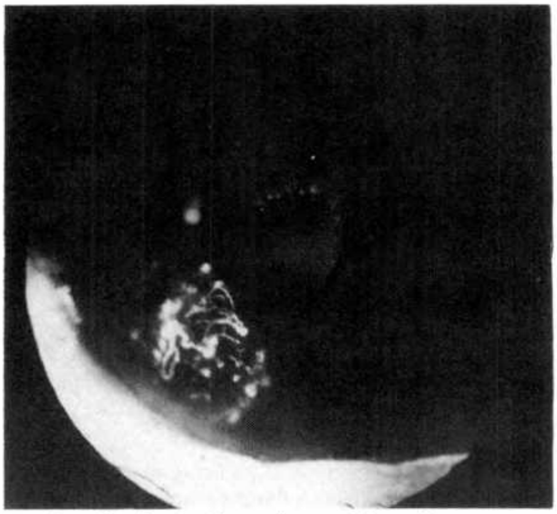

Fig. 2B *IFA showing incomplete masking and a disorganised vascular pattern.*

tumours in the malignant groups were younger than those with tumours showing benign characteristics ($p<0.001$). This would not be expected on the hypothesis that most tumours displaying malignant cytological features have transformed from benign lesions.[9]

Apart from the observation of rapid growth, clinical features are of little value in the prediction of tumour type.[1 3 4] Analysis of this small series confirmed that glaucoma, episcleral vascular dilatation, and sectoral cataract are features of ciliary body tumours, which are more commonly malignant than iris tumours. However, it is evident from a larger series that these features do not of themselves imply malignancy.[1] The only significant clinical findings were that very small tumours, of less than ¼ quadrant in area, were more likely to be benign ($p=0.029$) and that tumours involving the angle were more likely to be malignant ($p=0.019$). Because none of the tumours in this series exceeded 1 quadrant in area the effect of size was difficult to quantify. As angle involvement occurred in tumours of all sizes, the association of malignancy with tumour involving the angle is likely to be independent of size.

We found difficulty in interpreting our findings in the light of the previous reports because of two factors. Fluorescein angiograms could not neatly be fitted into the patterns described by Demeler,[3]

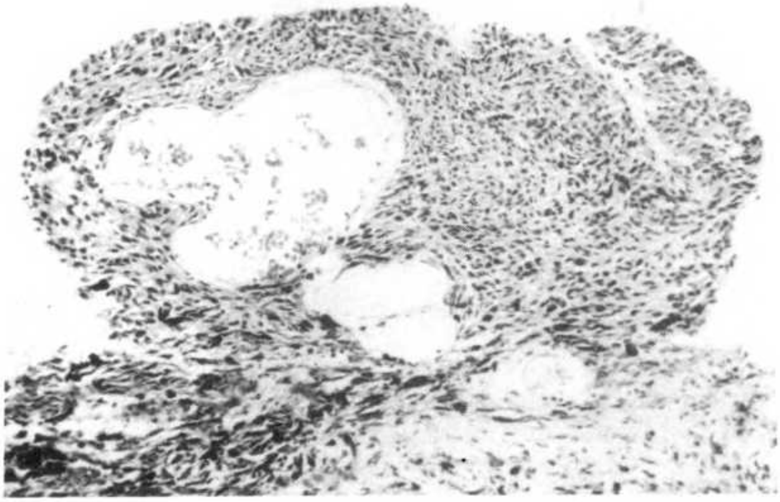

Fig. 2C *Histology shows a well demarcated plaque of small spindle cells protruding from the anterior surface of the iris. Note the prominent blood vessels. H and E, ×127.*

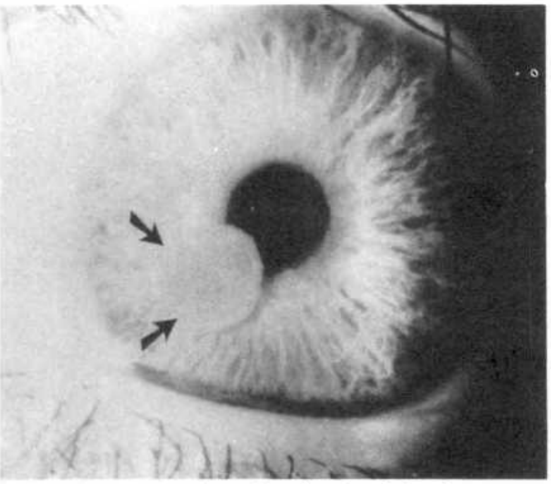

Fig. 3 *Case 18. Mixed spindle cell and epithelioid melanoma (iris).* A: *Clinical appearance of a vascular non-pigmented tumour associated with a distorted pupil and ectropion uveae.*

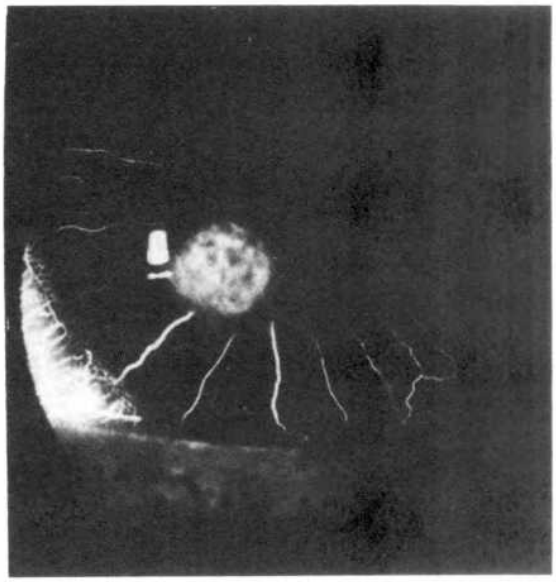

Fig. 3B *IFA shows early leakage from a geometric vascular pattern of vessels.*

Jakobiec *et al.*,[4] and Brovkina and Chichua,[6] though Kottow's[5] was comparable. Secondly, the criteria for the histopathological diagnosis of iris malignant melanomas have not been generally agreed; this problem has been fully discussed by Jakobiec *et al.*[14]

Our classification of IFA is simple, reasonably objective, and applicable to all tumours. It addresses the difficulty of having to categorise a borderline angiographic appearance that does not fit one of the previously described patterns, though it is impossible to avoid some degree of subjective assessment—that is, distinguishing between an organised and a disorganised vascular structure.

We failed to differentiate tumours in our inter-

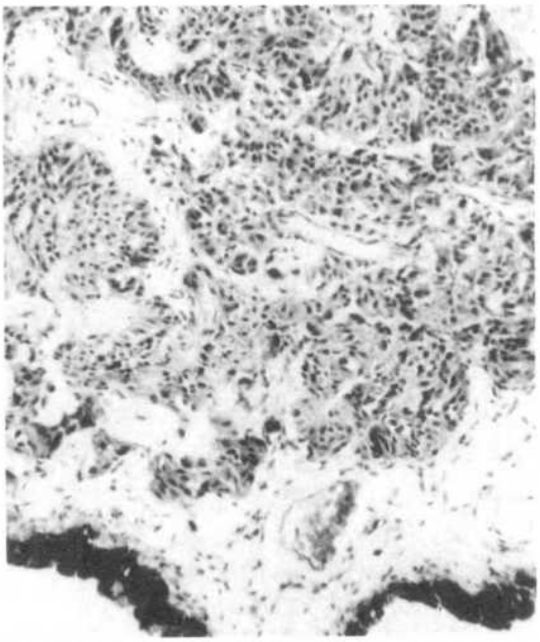

Fig. 3C *Histology shows that the iris stroma is infiltrated by a mixture of epithelioid and spindle cells. H and E, ×136.*

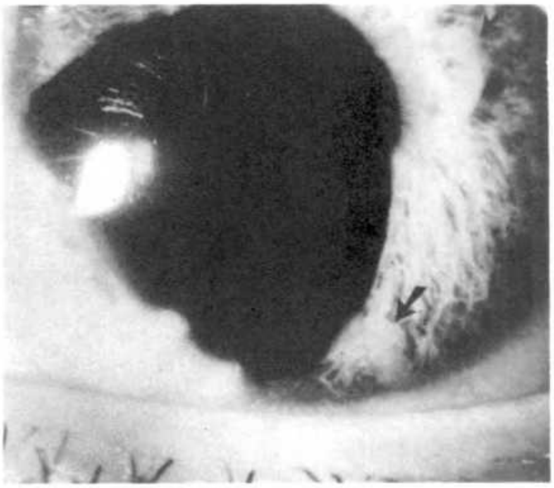

Fig. 3D *Clinical appearance of two metastatic lesions on the surface of previously uninvolved iris after broad iridectomy. These were removed with a vitreous cutter, and there has been no further recurrence during the past three years.*

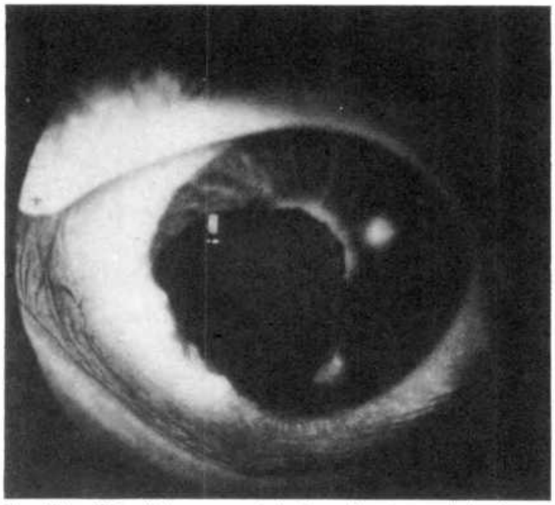

Fig. 3E *IFA of the metastatic lesions showing early leakage but no vascularity.*

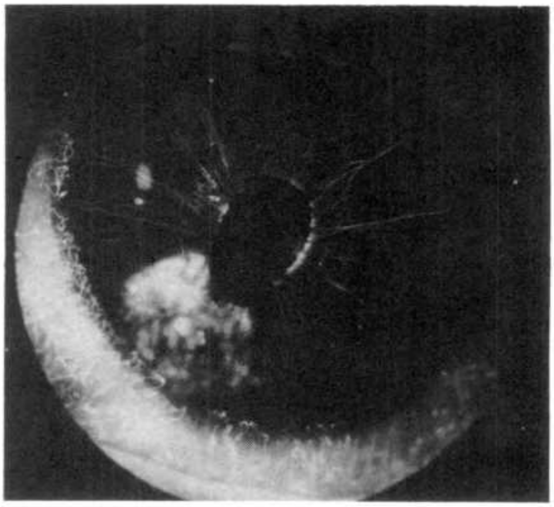

Fig. 4B *IFA showing early leakage and a geometric vascular pattern.*

mediate group from malignant tumours on the basis of IFA. We consider that our finding showing that the IFA characteristics of spindle cell naevus with surface plaque and borderline spindle cell naevus overlapped with those of the malignant group justifies our regarding tumours in groups 5 and 6 of the Jacobiec and Silbert classification with suspicion and assigning them to an intermediate group between benign and malignant.

Like other authors[1-6] we found two features that did not occur in benign tumours—a disorganised vascular pattern and gross late leakage. These features occurred only in 4/7 malignant tumours and in 2/6 intermediate tumours, so although there are no

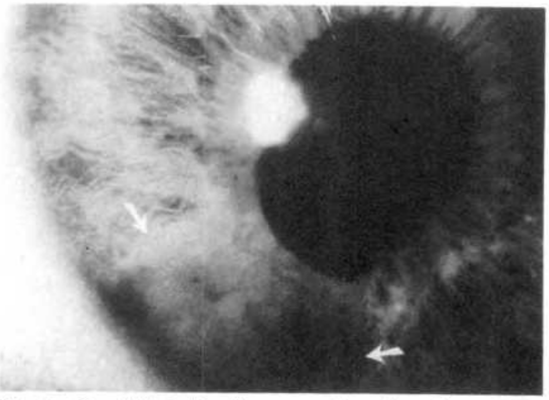

Fig. 4 *Case 9. Spindle cell naevus with surface plaque (iris). A: Clinical appearances of a tumour showing slight pigmentation, marked vascularisation involving the angle associated with distortion of the pupil, and ectropion uveae.*

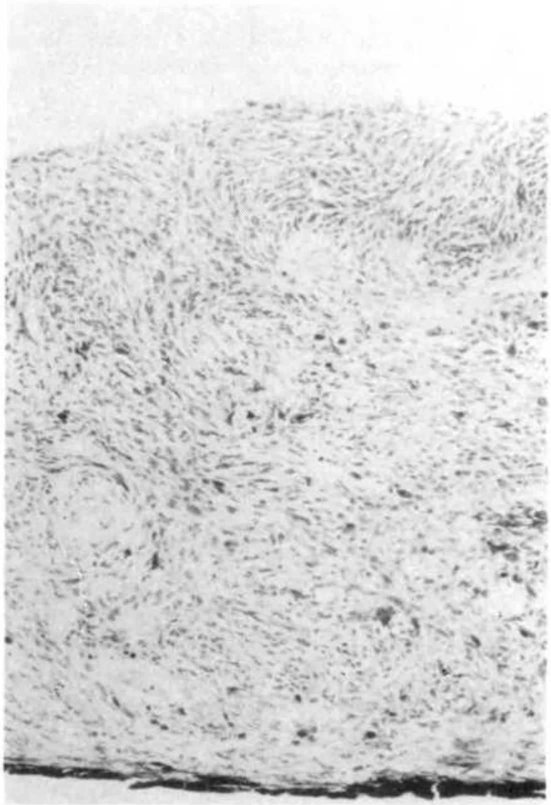

Fig. 4C *Histology shows that the stroma is largely replaced by a spindle cell naevus showing a more compact arrangement anteriorly to form a surface plaque. H and E, ×133.*

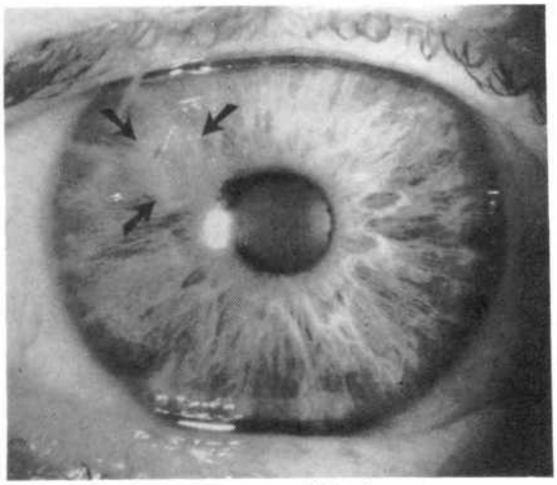

Fig. 5 *Case 14. Benign naevus. Clinical appearances unchanged in 66-month follow-up. No biopsy has been done.* A: *Clinical appearance showing a non-pigmented vascular tumour associated with ectropion uveae.*

false positives in our series these findings occur in only about half of the malignant tumours. Early leakage from permeable tumour vessels was found in all groups, although most commonly in malignant and intermediate tumours. It is probably a useful sign of aggressive tumour behaviour provided it is appreciated false positives may occur. The three malignant melanomas of the ciliary body displayed a different pattern from the malignant iris tumours by virtue of their large radial vessels. This is an observation of some importance, since just such a pattern was described in one series as being associated with benign behaviour.[4]

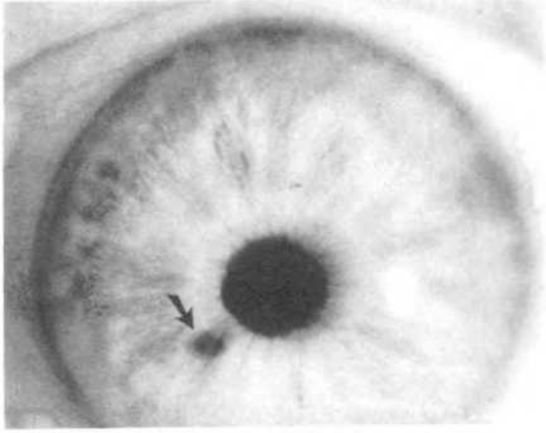

Fig. 6 *Case 13. Benign naevus. Clinical appearances unchanged in 90-month follow-up. No biopsy has been done.* A: *Clinical appearance showing a moderately pigmented tumour associated with iris freckles.*

Complete masking was the only feature shown exclusively by benign tumours. This has also been reported in all other series with the exception of one case[5] in which the histology was said to be malignant, although, unfortunately the histological criteria were not described. We do not consider that the experience of one incompletely substantiated case is sufficient cause to regard complete masking of fluorescence as an unreliable feature of benign tumours. Tumours showing a geometrically organised vasculature were found in all groups, and we cannot agree with Jakobiec *et al.*[4] or Brovkina and Chichua[6] that these are exclusively benign; one other author has recently described similar findings to ours in a further case.[9]

The other fluorescein features observed—

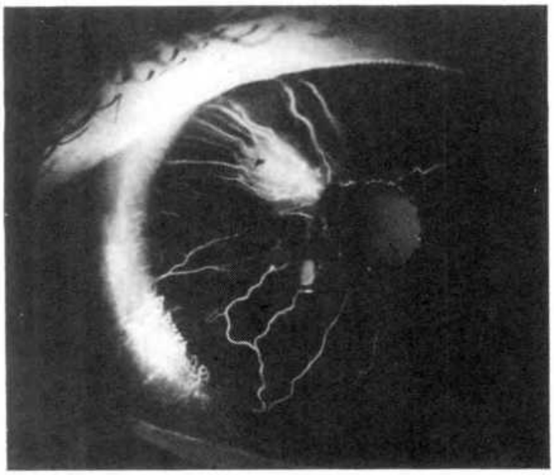

Fig. 5B *IFA shows early leakage and a geometric vascular pattern.*

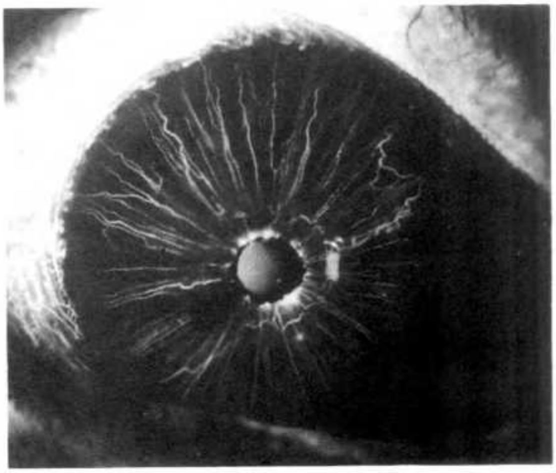

Fig. 6B *IFA shows complete masking of fluorescein.*

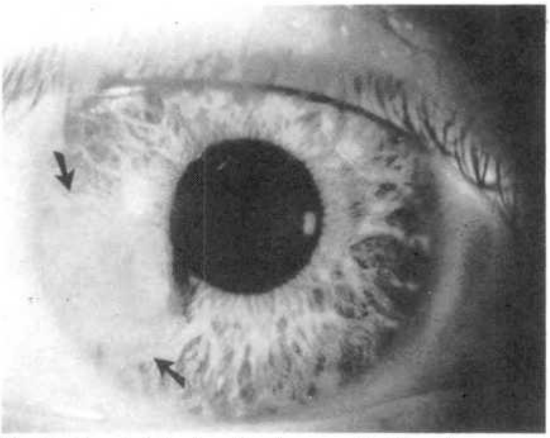

Fig. 7 *Case 5. Spindle cell melanoma.* A: *Clinical appearances showing a markedly vascular non-pigmented tumour involving the angle.*

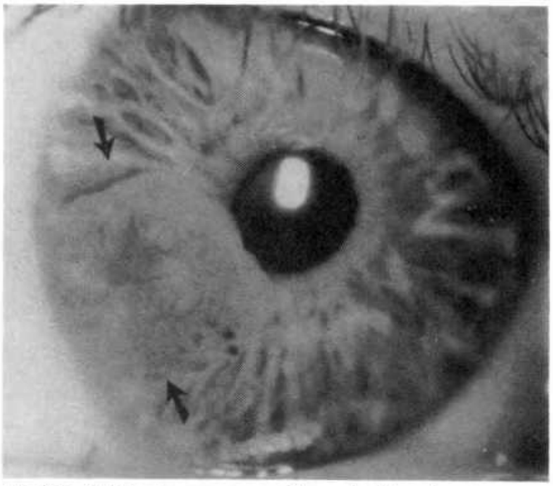

Fig. 7C *Clinical appearances 70 months later showing an increase in size that is documented on the IFA shown in 7D.*

intermediate degrees of masking or leakage, dilatation of radial vessels and the filling of a tumour in different phases—were not associated with any one tumour category but were common to all three groups. We could not substantiate the theoretical prediction that malignant tumours would have vessels that perfused out of phase with the main iris vasculature,[4] as this occurred in all groups.

Of the 11 patients that underwent repeated fluorescein angiography only three proved to be malignant. Although tumour growth was documented, in none of the cases did the fluorescein angiographic categorisation alter despite a follow-up period before surgery of 15–82 months. This is disappointing in view of the value of IFA in the follow-up of iris tumours that has been predicted, though not reported, by other authors.[3-5] This failure to demonstrate any IFA change is not surprising, because, although the long history of many of these lesions suggests that malignancies arise in previous naevi, patients probably present only when a change in appearance has occurred—that is, after malignant transformation has taken place.

It is to be expected that exceptions to our present findings will emerge in time. The inability to differentiate tumours of intermediate cytology from those with malignant cytology is a limitation of IFA and

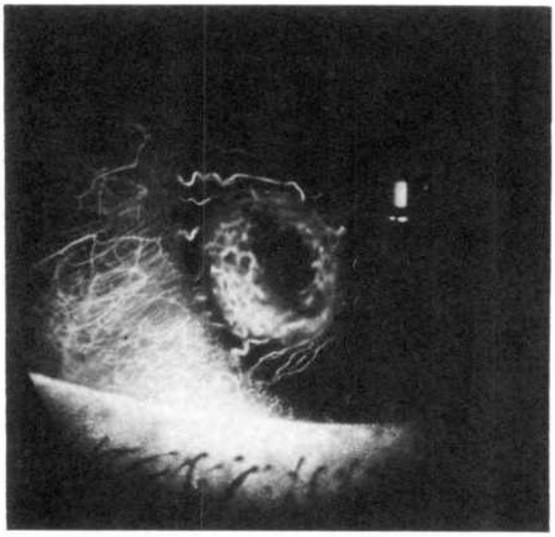

Fig. 7B *IFA showing incomplete masking, some late leakage, and a geometric vascular pattern.*

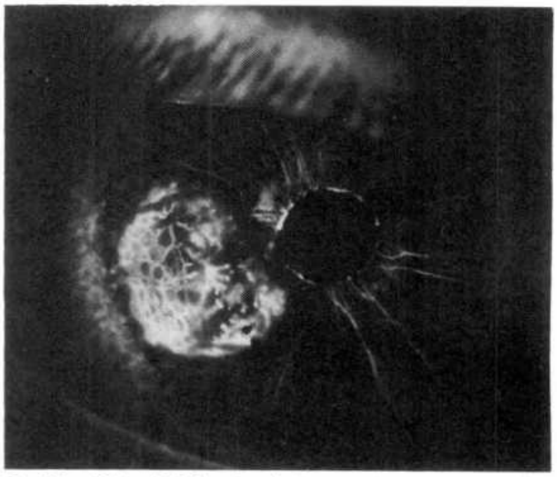

Fig. 7D *IFA of 7C showing the increase in size compared with 7B. The IFA classification of this tumour had not changed, however.*

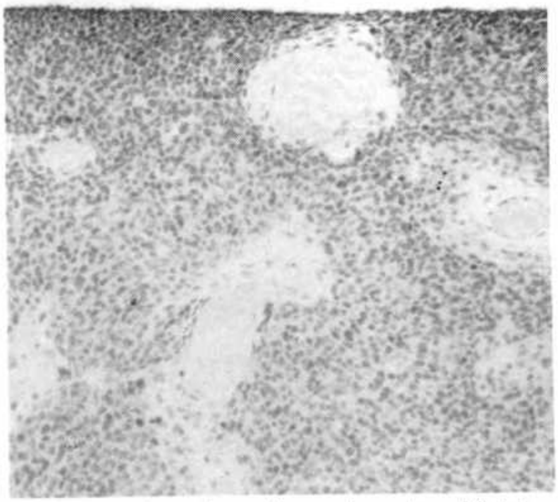

Fig. 7E *Histology of part of the anterior surface of the iris showing a uniform spindle cell melanoma with prominent vascularisation. H and E, ×127.*

reflects the problems of inferring tumour behaviour from the histology of these lesions. It is also known that benign progressive naevi may cause blindness by local growth and local invasion, although they have no metastatic potential.[1,10] The importance of identifying them before they become too large for simple surgical removal is obvious, and unfortunately IFA is unlikely to be able to identify these lesions.

At present the findings of a disorganised vasculature and gross leakage from tumour vessels indicates a tumour of malignant or intermediate cytology that demands careful follow-up. This occurred in 7/13 (53%) of such tumours in our series. The only pattern that has been shown by all authors to represent a benign lesion is complete masking of fluorescein without leakage, which was found in 4/9 (44%) tumours displaying benign behaviour in our series. Although we cannot endorse the assertion that IFA will yield reliable prognostic data in 90% of cases,[4] it did give useful information in 11/22 (50%) of the cases in our series. Other fluorescein patterns were found not to have enough specificity to give useful information.

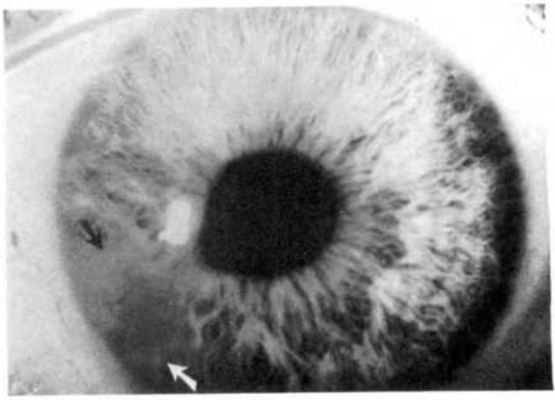

Fig. 8 *Case 33. Borderline spindle cell naevus (iris).* A: *Clinical appearances showing a vascular, moderately pigmented tumour involving the angle and associated with a distorted pupil.*

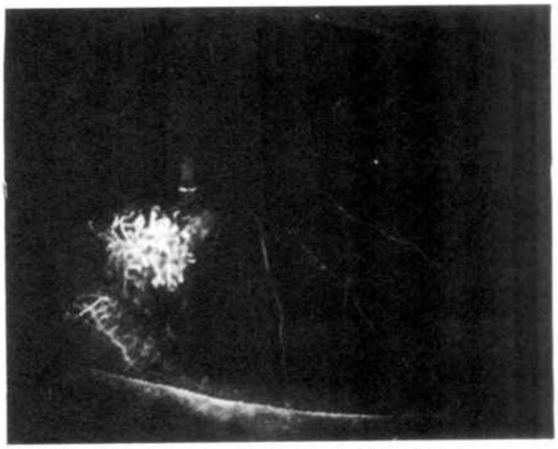

Fig. 8B *IFA showing a geometric vascular pattern.*

We thank the following for their assistance: S M Ford with the fluorescein and colour photography, Peter Clarke and David Powell for statistical advice, F Latif and R Emmett for secretarial help, and the Departments of Medical Illustrations at St Mary's Hospital and the Institute of Ophthalmology for preparing the illustrations.

References

1 Jakobiec FA, Silbert G. Are most iris melanomas 'really naevi'? *Arch Ophthalmol* 1981; **99:** 2117–32.

2 Noor Sunba MS, Rahi AHS, Morgan G. Tumours of the anterior uvea. 1. Metastasizing malignant melanoma of the iris. *Arch Ophthalmol* 1980; **98:** 82–5.

3 Demeler U. Fluorescence angiographical studies in the diagnosis and follow-up of tumours of the iris and ciliary body. *Adv Ophthalmol* 1981; **42:** 1–17.

4 Jakobiec FA, Depot MJ, Henkind P, Spencer WH. Fluorescein angiographic patterns of iris melanocytic tumours. *Arch Ophthalmol* 1982; **100:** 1288–99.

5 Kottow M. Fluorescein angiographic behaviour of iris masses. *Ophthalmologica (Basel)* 1977; **174:** 217–23.

6 Brovkina AF, Chichua AG. Value of fluorescein iridography in diagnosis of tumours of the iridociliary zone. *Br J Ophthalmol* 1979; **63:** 157–60.

7 Cheng H, Bron A, Easty D. A study of iris masses by fluorescein angiography. *Trans Ophthalmol Soc UK* 1971; **91:** 199–205.

8 Marsh RJ, Ford SM. Cine photography and video recording of anterior segment fluorescein angiography. *Br J Ophthalmol* 1978; **62:** 657–9.

9 Kersten RC, Tse DT, Anderson R. Iris melanoma. Nevus or malignancy? *Ophthalmology* 1985; **29:** 423–33.

10 Greer CH. *Ocular pathology*. 2nd ed. Oxford: Blackwell, 1972.

Accepted for publication 12 March 1987.

British Journal of Ophthalmology, 1988, 72, 338–343

Idiopathic bilateral lipid keratopathy*

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SUMMARY A 52-year-old Mexican man presented with asymptomatic, bilaterally symmetrical lipid infiltrates of the cornea and adjacent limbus. No evidence of previous ocular disease or systemic disorder of lipid metabolism could be detected. Penetrating keratoplasty of the right eye was required. The cornea was rigid and thick, with posterior bulging into the anterior chamber. Light microscopy revealed deep corneal lipid granules, foamy histiocytes, vascularisation, and chronic non-granulomatous inflammation. Transmission electron microscopy showed extracellular lipid spaces and numerous intracytoplasmic lipid vacuoles in histiocytes, keratocytes, conjunctival epithelium, and the endothelium of blood vessels in the corneal stroma and adjacent limbal conjunctiva. Histochemical analysis revealed the presence of neutral fats, free fatty acids, cholesterol, and phospholipids.

Opacification of the cornea due to the deposition of lipids may be primary without evidence of previous corneal vascularisation, or secondary to either pre-existing corneal disease with vascular exudation or systemic disturbances of lipid metabolism.[1-3]

We report an unusual case of idiopathic, bilaterally symmetrical lipid keratopathy associated with extensive neovascularisation, severe limbal involvement, and stromal lipid deposition.[4] The patient had no previous ocular disease or lipoprotein disorder; this suggests the primary nature of this condition.[5]

Case report

A 52-year-old Mexican man had a slowly progressive yellow infiltrate in the superior cornea of the right eye over a five-year period and a similar lesion for three years in the left eye. There were no associated symptoms and no history of ocular disease or trauma. The patient had been treated for hypertension with α-methyldopa (Aldomet) for two years. Laboratory values for serum cholesterol (3·70 mmol/l) and triglycerides (1·40 mmol/l) were normal. Serum lipid electrophoresis revealed no chylomicrons and normal patterns for β, pre-β, and α lipoproteins. Other laboratory values were normal and included the following: glucose 5·0 mmol/l, alkaline phosphatase 99 U/l, haemoglobin 166 g/l, haematocrit 49·5%, white blood count $9{\cdot}5\times10^{9}$/l, and a normal leucocyte differential count. The VDRL rest result was non-reactive. A chest *x*-ray and electrocardiogram were normal.

The best corrected visual acuities were hand motions in the right eye and 6/7·5 in the left eye. Slit-lamp examination of the right cornea revealed a yellowish white mass that occupied almost three-fifths of the superior cornea, including the visual axis (Fig. 1A). The superior limbus between the 10 and 2 o'clock positions was markedly elevated, and numerous, large, superficial, and deep stromal vessels extended into the abnormal corneal mass in this area (Fig. 1B). Clinically the entire thickness of the superior stroma was affected. In the left eye a

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*Part of this paper was presented by Dr Boruchoff at the Castroviejo Society Meeting, San Francisco, California, on 29 September 1985, and by Dr Alfonso at the Eastern Ophthalmic Pathology Society, Frenchman's Reef, St Thomas, on 1 November 1985.

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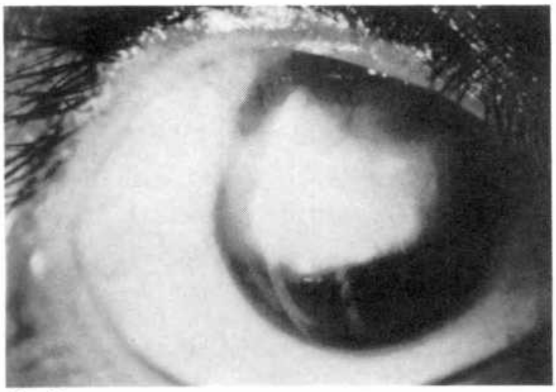
Fig. 1A

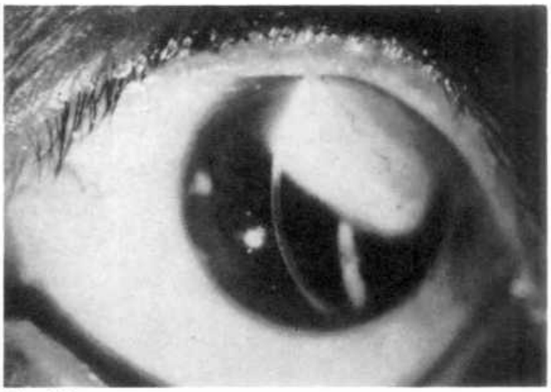
Fig. 1C

Fig. 1 A: *Right cornea with superior lipid infiltration extending into the visual axis.* B: *Thickening and vascularisation of superior limbal area of right eye.* C, D: *Left eye showing similar findings to right eye but without extension of lipid infiltrate into the visual axis.*

smaller lesion with similar characteristics was found (Figs. 1C, D). The other findings of the ocular examination were normal.

A central penetrating keratoplasty of the right eye was performed. At surgery the affected part of the cornea was rigid and bulged posteriorly into the anterior chamber and apposed the superior iris. The postoperative period was unremarkable, and there was no evidence of recurrence of the disorder at the six-month follow-up appointment.

HISTOPATHOLOGY

Specimens of limbal conjunctival biopsies and the 7·5 mm corneal button were obtained and trisected in the operating room. One fragment was placed in 2% glutaraldehyde and embedded in Epon, and thin sections were used for transmission electron microscopy. A second fragment was fixed in 10% buffered formaldehyde, embedded in paraffin, sectioned, and stained with haematoxylin and eosin, periodic acid-Schiff, Congo red, and alcian blue. A third fragment was frozen at −70°C, sectioned, postfixed in 37% formaldehyde fumes for 15 minutes, and stained for fats.

LIGHT MICROSCOPY

The conjunctival specimen consisted of a connective tissue fragment lined by non-keratinised squamous epithelium of normal thickness and showed mild to moderate intracellular oedema of the basal cell layer. Moderate numbers of goblet cells were present. The substantia propria contained blood vessels, rare plasma cells, and lymphocytes.

The corneal specimen was thickened posteriorly (Fig. 2A). The corneal epithelium showed moderate oedema of the basal cell layer. At the periphery a fibrocellular pannus was interposed between the epithelium and the intact Bowman's layer. The superficial stroma was normal. The deep stroma was extremely thickened, especially centrally, with

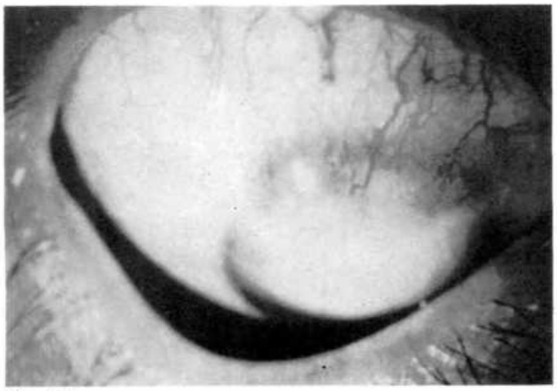
Fig. 1B

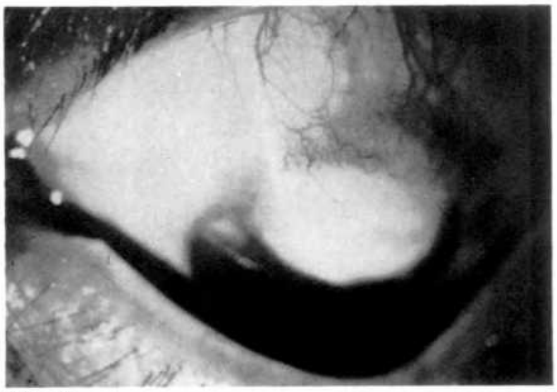
Fig. 1D

Fig. 2A *Right eye. Thickening and posterior bulging of corneal specimen caused by lipid and inflammatory infiltrate (haematoxylin and eosin, ×5).*

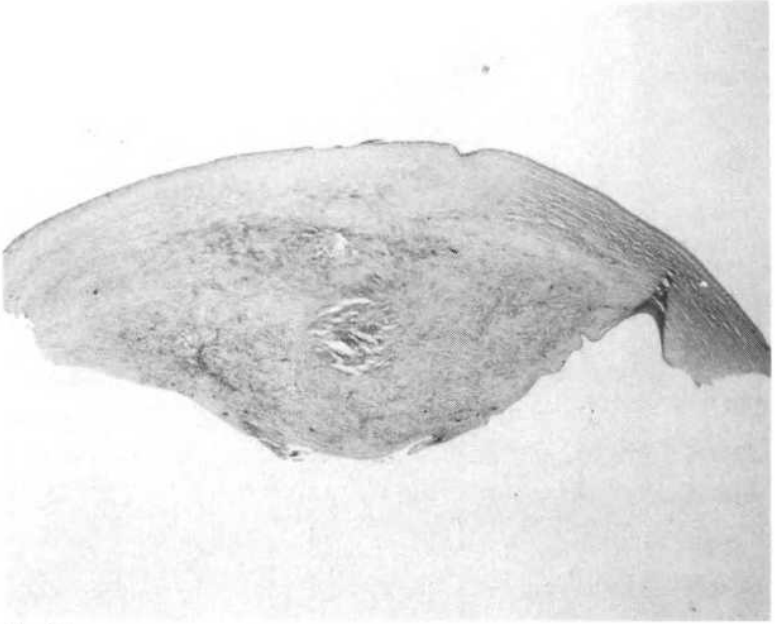

Fig. 2A

moderate vascularisation and disorganisation of the collagen fibrils (Fig. 2B). This area was heavily infiltrated by lipid laden histiocytes, lymphocytes, and plasma cells. Scattered epithelioid cells were also present. Descemet's membrane appeared intact. The corneal endothelium contained focal areas of pigment deposition.

TRANSMISSION ELECTRON MICROSCOPY

The conjunctival epithelium contained both intra-

Fig. 2B *Posterior cornea showing vascularisation and disorganisation of collagen lamellae. The infiltrate consisted of lipid laden histiocytes, lymphocytes, plasma cells, and epithelioid cells (haematoxylin and eosin, ×15).*

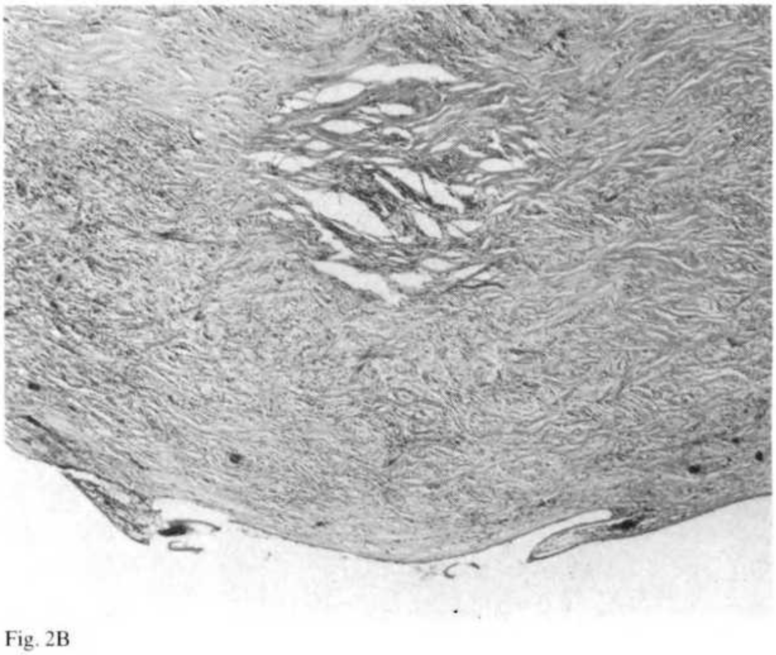

Fig. 2B

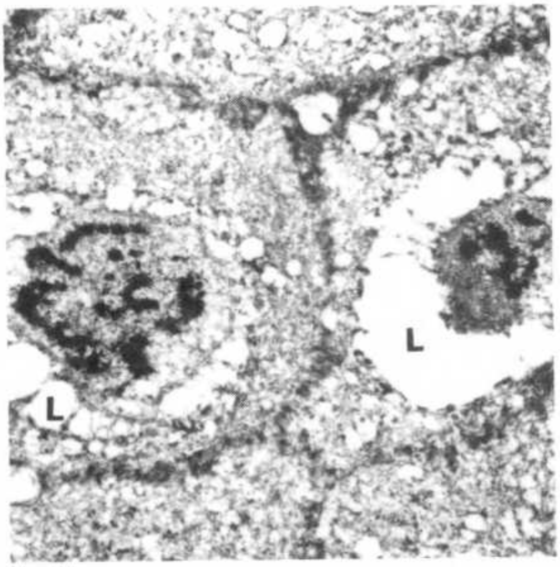

Fig. 3A

Fig. 3 *Transmission electron microscopy of the right eye, showing spaces where lipids* (L) *had dissolved.* A: *Conjunctival epithelium (×6130).* B: *Marked degenerative changes in keratocytes (arrow) and collagen lamellae* (C) *(×7710).* C: *Histiocyte, containing rough endoplasmic reticulum* (ER) *and red blood cell* (RBC) *(×9390).* D: *Vascular endothelium and intravascular red blood cells* (RBC) *(×8000).*

cellular vacuoles and extracellular spaces, which probably contained lipids prior to fixation (Fig. 3A).

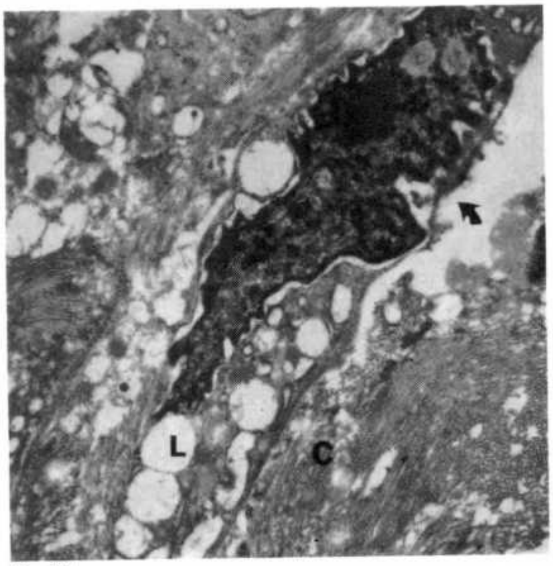

Fig. 3B

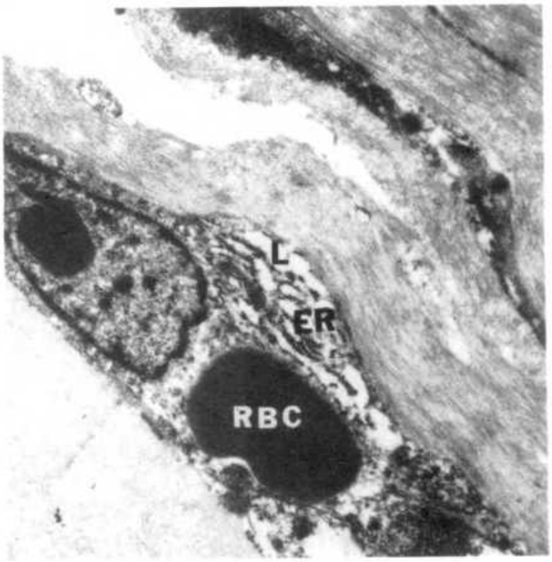

Fig. 3C

The substantia propria and vascular endothelium also contained 'lipid' spaces.

In the cornea there were marked degenerative changes in the keratocytes and disruption of the posterior collagen lamellae (Fig. 3B). Histiocytes and neovascular endothelium were vacuolated extensively (Figs. 3C, D), and adjacent keratocytes (Fig. 3D) were pyknotic.

HISTOCHEMICAL EXAMINATION

After sectioning and postfixing the frozen tissue in

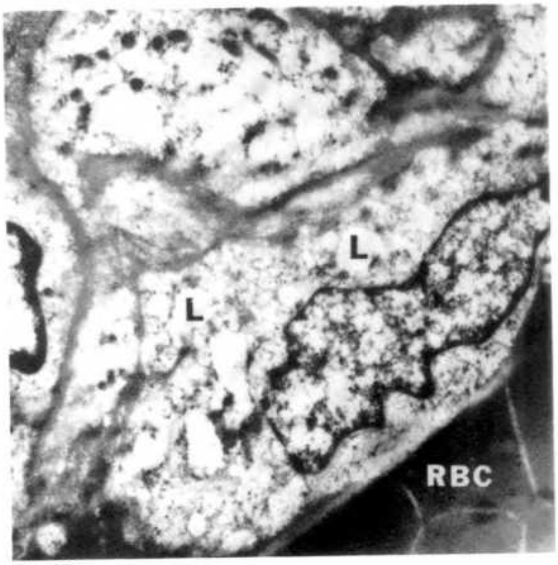

Fig. 3D

Table *Histochemical data*

Stain	*Substance tested for*	*Result*
Congo red	Amyloid	Negative
Masson trichrome	Collagen	Negative
Alcian blue	Acid mucopolysaccharide	Negative
Periodic acid-Schiff	—	Negative
Alizarin red	Calcium	Negative
Oil-red-O	Triglycerides, neutral fats	Positive
Sudan black B	Neutral fats, phospholipids	Positive
Baker	Phospholipids, galactolipids	Positive

formalin fumes we noted that the area of corneal infiltration was somewhat birefringent. No abnormal staining was observed with alcian blue, Masson trichrome, Congo red, periodic acid-Schiff, and bacterial and fungal stains. The alizarin stain was negative. The Baker, Sudan black B, and oil-red-O stains were positive for both intracellular and extracellular fat. The material was interpreted as consisting of neutral fats, free fatty acids, cholesterol crystals, and small amounts of phospholipids (Table).

Discussion

Deposition of lipids in the cornea has been described in several pathological conditions,[4] including lipid keratopathy, lipoidal degeneration, Schnyder's crystalline dystrophy, corneal xanthoma, corneal arcus, and corneal xanthogranuloma. Occasionally lipids may be deposited in the cornea secondary to systemic lipoprotein disorders (reviewed by Schaefer[3]), including Tangier disease, lecithin cholesterol acyltransferase deficiency, and familial high-density lipoprotein deficiencies. In lipoprotein disorders the involvement is usually bilateral, but corneal vascularisation is absent.

Corneal arcus, a lipid infiltration of the paralimbal cornea adjacent to Bowman's layer and Descemet's membrane, is thought to be part of the normal aging process in patients over 50 years old. An association with hyperlipoproteinaemia in patients under the age of 40 is controversial. The lipoprotein infiltration of corneal arcus is primarily extracellular, with no associated cellular degeneration or inflammation. Corneal arcus appears clinically as peripheral grey areas separated from the limbus by a lucid interval, but limbal vasculature, corneal temperature, and local blood flow modify the lipid deposition.[6] Fine and associates have reported a case of primary lipoidal degeneration of the cornea associated with arcus senilis.[7]

Abnormal proliferation of lipocytes can lead to lipid deposition in the cornea in conditions such as juvenile xanthogranuloma. Raised limbal dermoids should also be included in the differential diagnosis.

Cogan and Kuwabara coined the term lipid keratopathy to describe the deposition of fatty plaques in or adjacent to areas of abnormal corneal vascularisation.[4] In their review of the literature they cited reports that used various terms, such as fatty dystrophy of the cornea, dystrophia adiposa corneae, adiposis of the eye, xanthomatosis, lipid-interstitial keratitis, lipidosis corneae, and secondary steatosis. The pathogenesis of lipid keratopathy, as described by these authors, is related to prior vascularisation of the cornea due to trauma or inflammation, leading to lipid exudation in areas adjacent to the vessels. Argon laser ablation of the vascular channels may arrest the process of lipid deposition and occasionally aid in resolving the lipid infiltrate.[8] Experimentally induced corneal vascularisation can also lead to fatty infiltration of the cornea.[9]

Several cases of corneal lipid deposition not associated with previous eye trauma, inflammation, or systemic disorders of lipid metabolism have been reported.[10-12] Baum[10] described a 72-year-old woman with unilateral lipid infiltration of the cornea, associated with a slight limbal conjunctival injection. A few deep blood vessels extended into the lesion from the adjacent corneoscleral limbus. Thin-layer and gas-liquid chromatography detected the presence of cholesterol but no other lipids.

A case of an asymptomatic 31-year-old man reported by Barishak and Stein[11] had a unilateral corneal lipid infiltration similar in clinical appearance to that of our patient. Vascularisation was present in the lesion as well as in the adjacent corneoscleral limbus. The plaque contained mostly cholesterol and neutral fats, with cholesterol esters and fatty acids present in small quantities.

Our patient shares several clinical features with other cases.[10-12] No systemic or ocular disorder was present to explain the lipid deposition in the cornea in any of the four patients, yet they showed severe vascularisation of the cornea and adjacent corneoscleral limbus. No symptoms of ocular inflammation had been present prior to or at the time of initial examination. Our case is analogous to that of Croxatto *et al.*[12] in its insidious, bilaterally symmetrical presentation and thickened, rigid corneas.

Lipid keratopathy may be associated with concurrent symptoms of ocular inflammation with systemic abnormalities of lipid metabolism. For example, Friedlaender and associates reported a case of a 55-year-old woman with bilateral lipid infiltrates of the cornea,[13] who differed from our patient in having a mildly raised blood cholesterol level and clinical evidence of ocular inflammation, including pain, photophobia, central corneal epithelial defects, and a diffuse erythematous rash on the face, chest, and hands. Jack and Luse[14] described a 51-year-old woman with raised blood triglycerides who had an asymptomatic corneal lipid deposition in an area of a previously excised pterygium.

In contrast most other cases of lipid keratopathy directly complicate corneal neovascularisation following trauma or keratitis and are associated commonly with a systemic disorder of lipid metabolism;[13 14] these conditions are classified as secondary lipid keratopathies. The absence of previous ocular disease and the apparently normal premorbid corneas in the present case and in those of Baum,[10] Barishak and Stein,[11] and Croxatto *et al.*[12] suggest that these cases should be classified as primary lipid keratopathies (idiopathic). The remarkable symmetry and disease pattern of our case and that of Croxatto *et al.*[12] also provide support for a primary rather than a secondary cause.

The nature of the process in the idiopathic cases is unclear. Low-grade inflammation at the corneoscleral limbus or ocular surface, which was unnoticed by the patient but caused corneal vascularisation and subsequent lipid deposition, is one possible explanation. The finding in our case and others[11] of 'lipid' spaces in the vascular endothelium of the lesion and adjacent conjunctiva could represent a primary functional defect of the vascular endothelial cells with leakage of fats into the adjacent corneal tissues. This is turn could induce secondary inflammation followed by corneal vascularisation and further fat exudation.[4] Cogan and Kuwabara[15] and Jack and Luse[14] proposed that a derangement of corneal cells might lead to necrosis and exposure of intracellular fatty material as the initial event leading to inflammation, vascularisation, and further deposition of fats into the corneal stroma. This derangement might be caused by an intrinsic defect, inflammatory toxins, or trauma.

In animal models experimentally induced corneal vascularisation sometimes progresses to lipid exudation into the adjacent corneal tissue, though hypercholesterolaemia in the early phases of neovascularisation is usually a necessary precondition of experimental lipid keratopathy. The beagle[5] and Cuban tree frog (Albert DM, personal communication, 1986), however, provide animal models of naturally occurring primary lipid keratopathy. Further laboratory investigations are required to clarify these pathophysiological questions as to the nature of lipid keratopathy in humans.

In our case histochemical analysis of the corneal button revealed the presence of neutral fats, free fatty acids, cholesterol, and a small amount of phospholipids. Barishak and Stein[11] found cholesterol and neutral fats, and Baum[10] only cholesterol, in their cases. Croxatto and colleagues[12] found neutral fats, cholesterol, and phospholipids. In cases of corneal lipid deposition, corneal and plasma lipids should be analysed comparatively to ascertain whether a systemic metabolic fat abnormality is the cause.

David G Cogan, MD, and Lorenz Zimmerman, MD, reviewed the histopathological slides. Robert R McMukin, MD, and Ian W McLean, MD, examined the sections stained for lipids. Diego Cuevas Cancino, MD, provided clinical information. This study was supported in part by the Heed/Knapp Féllowship (1984–6), EY05769 (NIH), and National Society for the Prevention of Blindness (Dr Alfonso).

References

1 West C. Corneal disease. In: Peyman GA, Sanders DR, Goldberg MF, eds. *Principles and practice of ophthalmology*. Philadelphia: Saunders, 1980: 410–2.

2 Smolin G. Dystrophies and degenerations. In: Smolin G, Thoft RA, eds. *The cornea: scientific foundations and clinical practice.* Boston, Little, Brown, 1983: 333.

3 Schaefer EJ. Clinical, biochemical, and genetic features in familial disorders of high density lipoprotein deficiency. *Arteriosclerosis* 1984; 4: 303–22.

4 Cogan DG, Kuwabara T. Lipid keratopathy and atheroma. *Trans Am Ophthalmol Soc* 1958; **56:** 109–22.

5 Roth AM, Ekins MB, Waring III GO, Gupta LM, Rosenblatt LS. Oval corneal opacities in beagles. III. Histochemical demonstration of stromal lipids without hyperlipidemia. *Invest Ophthalmol Vis Sci* 1981; **21:** 95–106.

6 Fielder AR, Winder AF, Sheraidah GAK, Cooke ED. Problems with corneal arcus. *Trans Ophthalmol Soc UK* 1981; **101:** 22–6.

7 Fine BS, Townsend WM, Zimmerman LE, Lashkari MH. Primary lipoidal degeneration of the cornea. *Am J Ophthalmol* 1974; **78:** 12–23.

8 Marsh RJ, Marshall J. Treatment of lipid keratopathy with the argon laser. *Br J Ophthalmol* 1982; **66:** 127–35.

9 Stock EL, Mendelsohn AD, Lo GG, Ghosh S, O'Grady RB. Lipid keratopathy in rabbits: an animal model system. *Arch Ophthalmol* 1985; **103:** 726–30.

10 Baum JL. Cholesterol keratopathy. *Am J Ophthalmol* 1969; **67:** 372–5.

11 Barishak YR, Stein R. Lipid keratopathy. *Ann Ophthalmol* 1974; **6:** 377–80.

12 Croxatto JO, Dodds CM, Dodds R. Bilateral and massive lipoidal infiltration of the cornea (secondary lipoidal degeneration). *Ophthalmology* 1985; **92:** 1686–90.

13 Friedlaender MH, Cavanagh HD, Sullivan WR, Gallagher MJ, Dickersin GR. Bilateral central lipid infiltrates of the cornea. *Am J Ophthalmol* 1977; **84:** 781–7.

14 Jack RL, Luse SA. Lipid keratopathy: an electron microscopic study. *Arch Ophthalmol* 1970; **83:** 678–91.

15 Cogan DG, Kuwabara T. Lipogenesis by cells of cornea. *Arch Pathol* 1955; **59:** 453–6.

Accepted for publication 5 March 1987.

British Journal of Ophthalmology, 1988, **72**, 344–347

Depth measurement with the slit-lamp microscope

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SUMMARY The sagittal distance of ocular structures can be obtained with a slit-lamp microscope providing the movement of the slit-lamp can be measured. A simple device consisting of a pointer attached by a spring clip to the axle of a Haag-Streit 900 slit-lamp is described. The pointer rides over a scale which slides with the slit-lamp. Comparisons of anterior chamber depth and lens thickness showed a high correlation between this optical method and ultrasound measurements.

During studies on the influence of environmental and other factors concerned in the development of cataract it became clear that it was important to extend these studies to the earliest stages of cataract formation. One feature of many cataracts is a reduction in sagittal thickness of the lens, and such a measurement provides a more objective assessment than describing slit-lamp microscope appearances. The present study was undertaken to design a simple, rapid means of measuring lens thickness which could be used in population surveys.

The sagittal distance of structures within the eye can be measured by a variety of special instruments such as the Goldmann pachymeter[1] for the cornea and anterior chamber, Stenstrom's[2] optical method, slit-lamp photography using the Scheimpflug principle[3 4] and ultrasonography. When such special instruments are not available, the movement of the viewing system of a slit-lamp microscope can be used to measure the apparent depth of structures by focusing first on the anterior surface of the structure and measuring the movement required to focus on the posterior surface. In older models of the slit-lamp this movement could be measured by means of an Ulbrich drum, but this is not possible with modern slit-lamps, in which the viewing and illumination system is controlled by a joy stock. Krannig[5] described a method of measuring the movement of such instruments by marking a strip of paper in the two positions of focus and claimed an accuracy of ±0·3 mm. Magnification of the movement should enable greater accuracy, and a simple apparatus designed for the Haag-Streit 900 slit-lamp is described.

Material and methods

The Haag-Streit 900 is mounted on perforated roller bearings running on plates with indentations fitting the perforations. The bearings are 40 mm in diameter, so that for a rotation of 360° the sagittal movement is $40\times\pi=125{\cdot}66$ mm or 0·349 mm/degree of rotation. By fixing a pointer by a spring clip to the axle and using a protractor with a radius of 10 cm the angular movement can be measured to at least 0·5°. The protractor is mounted on a piece of Plexiglass with a footplate and a cut-out to go over the axle, so that the protractor slides backwards and forwards with the slit-lamp. In practice it was found to be more convenient to use a millimeter scale glued to the edge of a 2·5 mm thick sheet of methyl methacrylate with a pointer riding over the scale (Figs. 1, 2). With this arrangement 1 mm on the scale represented a 0·2 mm movement of the slit-lamp.

In use the patient is seated at the slit-lamp with the head resting firmly on the headrest. The slit-lamp is focused on the anterior surface of the cornea and the pointer brought back to zero by means of an adjustable stop. The slit-lamp is then advanced to focus on the anterior surface of the lens and the scale reading noted. This manoeuvre is repeated until consistent readings are obtained.

For measurement of the thickness of the lens the slit-lamp is focused on the anterior lens surface and the pointer zeroed. The slit-lamp is then moved to focus on the posterior lens surface and the reading noted.

With this apparatus it is possible to measure the apparent depth of the anterior chamber and apparent thickness of the lens to ±0·2 mm. Several measure-

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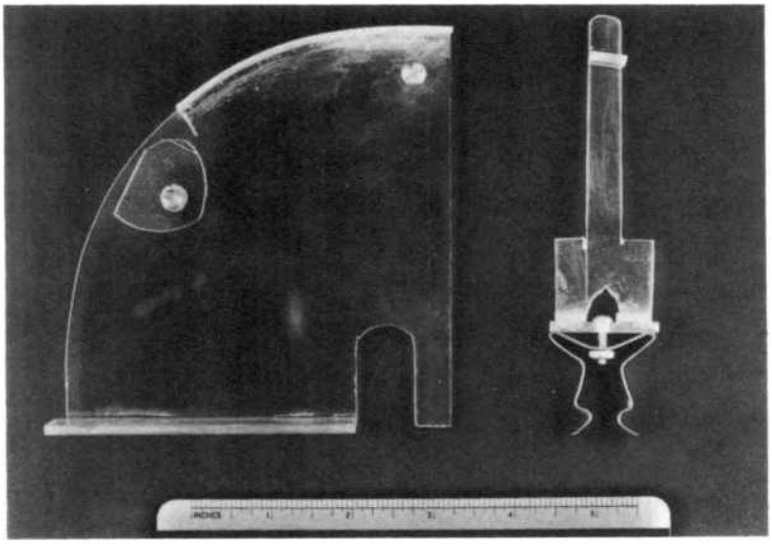

Fig. 1 *Plexiglass plate with scale and cut-out for the axle of the slit-lamp and the pointer with spring clip.*

ments can be made quickly until a repeatable reading is obtained. If the angle between the slit and the microscope is small, the thickness of the lens can be measured through an undilated pupil.

The relationship between the true depth and the apparent depth of the anterior chamber can be calculated according to Linstedt[6] from the equation:

$$\text{True depth} = \frac{r \times n \times X}{r + (n-1)\,X}$$

where r = radius of curvature of the cornea,
n = refractive index of aqueous,
X = apparent depth.

The apparent depth of the anterior chamber was measured in 70 eyes and the lens thickness measured in 46 eyes with clear lenses. Ultrasonic biometry with a Storz Alpha 20/20 biometric ruler was also done on these eyes and the results were compared with the optical measurements.

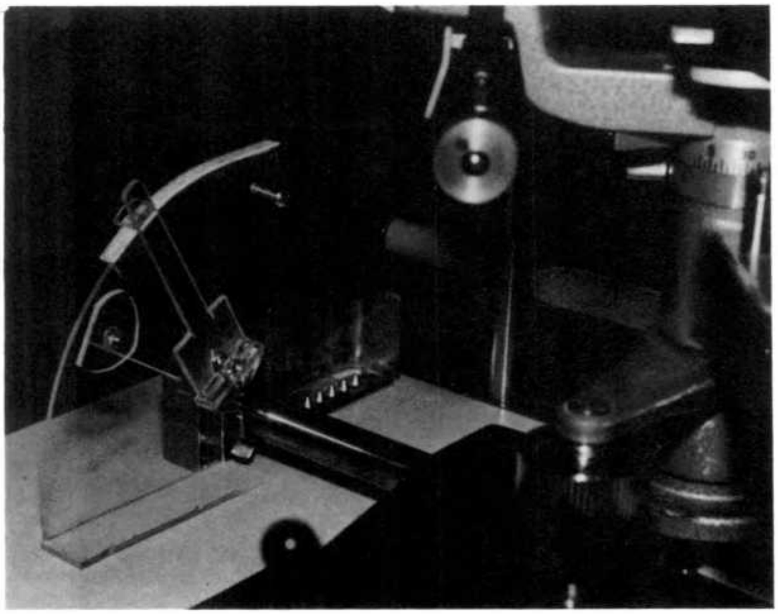

Fig. 2 *The apparatus attached to the slit-lamp microscope.*

Results

ANTERIOR CHAMBER DEPTH

The slit-lamp measurements were corrected by means of Linstedt's formula assuming a mean anterior corneal radius of 7·8 mm and a refractive index of 1·34 for the aqueous. The mean difference between the optical and ultrasound measurements was 0·16±0·3 mm, the ultrasound measurements being higher by this amount. The mean anterior chamber depth by the optical method was 3·04±0·54 mm and the mean of the ultrasonic measurements was 3·27±0·41 mm. This difference is statistically significant ($p<0{\cdot}01$), but probably not clinically significant.

Linear regression analysis between the ultrasound and optical readings gave a correlation coefficient of $r=0{\cdot}77$ with a slope of 0·84 and intercept of 0·34. The results for all right eyes are shown in Table 1.

CLEAR LENSES

A comparison of the ultrasound and apparent thickness of the lens by linear regression analysis gave a correlation coefficient of 0·86 with a slope of 0·99 and an intercept of 0·25, so that there were only small differences between the ultrasound measurements and the apparent thickness as measured with the slit-lamp. The results for all right eyes are shown in Table 2.

Table 1 *Comparison of ultrasonic and optical measurements of anterior chamber depth*

Ultrasonic	*Optical*	*Ultrasonic*	*Optical*
3·9	3·55	3·3	2·91
3·8	3·34	3·0	2·69
3·2	3·55	2·8	2·69
3·4	3·13	4·1	3·97
3·9	4·17	3·5	3·34
3·7	3·13	3·5	3·55
3·3	3·02	3·8	3·13
3·0	2·69	3·6	2·91
3·5	3·13	2·6	2·91
3·4	2·91	3·3	3·34
2·6	2·46	3·5	3·14
3·8	3·34	3·1	2·69
3·1	3·34	3·2	2·91
3·1	3·34	3·4	3·34
3·1	2·91	3·4	3·34
3·6	3·13	3·0	2·91
3·0	3·13	2·8	2·46
3·0	2·91	3·2	2·91
4·0	4·17	3·4	3·55
3·6	3·13	2·8	2·46
3·1	3·13	3·5	3·55
3·7	3·34	2·4	2·24
3·8	3·76	3·0	2·69
2·9	3·13	2·8	2·69
2·7	2·91	3·4	2·91
3·1	2·69	2·6	2·91
3·2	2·91	3·9	3·34
3·8	3·76	3·1	3·51
3·1	2·91	3·3	2·22
3·2	2·91	3·2	2·66
3·2	3·13	3·0	2·44
3·9	3·34	3·0	2·44
3·6	4·27	2·8	2·44
3·9	3·97	2·9	2·44
2·9	2·91		

Table 2 *Comparison of ultrasonic and optical measurements of lens thickness*

Ultrasonic	*Optical*	*Ultrasonic*	*Optical*
4·1	5·0	4·1	4·0
4·4	4·1	4·4	4·6
3·6	3·6	3·8	4·2
4·5	4·8	3·7	3·8
3·9	4·0	4·7	4·8
4·5	4·6	4·7	4·8
4·1	4·0	4·6	4·8
4·9	5·2	4·1	4·0
4·3	4·6	4·1	4·2
4·1	4·3	3·6	3·6
4·8	5·0	3·5	3·4
3·1	3·4	4·7	5·2
4·2	4·0	4·7	5·2
4·3	4·4	4·4	4·4
4·3	5·0	4·3	4·4
4·5	4·8	3·5	3·6
4·9	4·6	4·4	4·0
4·3	4·4	4·6	4·8
3·9	4·6	4·1	4·6
4·2	4·4	4·3	4·6
4·8	5·4	4·4	4·6
4·0	4·6	4·8	4·8
4·1	4·2	4·8	5·0
5·3	5·2		

Discussion

These results suggest that there is a good correlation between depth measurements obtained by measuring the movement of a slit-lamp microscope and those obtained by ultrasound. The agreement is not quite so good for anterior chamber depth as for lens thickness, possibly because individual corneal curvature measurements were not done and the calculations were based on a mean value of 7·8 mm.

Krogsaa *et al.*[7] calculated the ratio of the intraocular distance divided by the corresponding slit-lamp movement for the anterior chamber, the lens, and the vitreous body. Their calculations were based on Gullstrand's emmetropic eye with a Goldmann fundus contact lens in place, so that the optical conditions were not the same as measurements made without a contact lens. They reported a ratio of 1·45 between the intraocular distance and the slit-lamp movement for the anterior chamber and a ratio of 1·64 for the lens. My measurements without a contact lens gave a ratio of 1·54 for the anterior chamber and 1·02 for the lens. The figure for the anterior chamber is fairly close to their calculated value, but the ratio for the lens is considerably less. It is certainly rather surprising that the apparent thickness of the lens as measured from the movement of the slit-lamp should be almost the same as the values obtained by ultrasonic biometry; this is presumably due to the smaller difference in refractive index between the aqueous and the lens and that of air and the aqueous. If a value of 0·963 (the difference between the refractive index of aqueous and refractive index of the lens) is used for n in Linstedt's formula, the ratio between the intraocular distance and slit-lamp movement is 0·95—much closer to the present results.

The primary purpose of this study was to see if a simple optical method of measuring lens thickness was sufficiently accurate for use in population surveys where more elaborate methods might not be feasible. The reported results suggest that measurement of slit-lamp movement compares well with ultrasonic biometry. The movement could be measured electronically with, for example, a potentiometer as was done by Krogsaa *et al.*,[7] but the method described here is simple to zero and gives a direct reading.

A similar apparatus to that described for the Haag-Streit slit-lamp could also be devised for other slit-lamps which employ roller bearings.

This research was supported in part by an unrestricted grant from Research to Prevent Blindness. Statistical analysis was done by Ms Shu-Jane Tan of the Department of Preventive Medicine, University of Iowa.

References

1 Goldman H. Ein neuer Messokular für die spaltlampe. *Ber Dtsch Ophthalmol Ges* 1932; **49:** 435–7.
2 Stenstrom S. An apparatus for measuring the depth of the anterior chamber, based on Linstedt's principle. *Acta Ophthalmol (Kbh)* 1953; **31:** 265–70.
3 Goldmann H. Eine Methode zur Volumbestimmung der Vorderkammer des lebenden Menschen. *Ophthalmologica* 1941; **102:** 7–12.
4 Brown N. Slit-lamp photography. *Trans Ophthalmol Soc UK* 1969; **89:** 397–408.
5 Krannig D. Vereinfachte Tiefenmessung, insbesondere am vor deren Augapfl. *Ber Dtsch Ophthalmol Ges* 1956; **60:** 296–7.
6 Linstedt F. Über die Messung der Tiefe der vorderen Augenkammer mittels eines neun für klinischen Gebrauch bestimmen Instrument. *Arch Augenheilkd* 1916; **80:** 104–67.
7 Krogsaa B, Fledelius H, Larsen J, Lund-Andersen H. Photometric oculometry. 1. An analysis of the optical principles in slit-lamp fluorophotometry. *Acta Ophthalmol (Kbh)* 1984; **62:** 274–89.

Accepted for publication 5 March 1987.

British Journal of Ophthalmology, 1988, 72, 348–353

Lens thickness in early cataract

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SUMMARY The search for environmental factors associated with cataract has produced conflicting evidence and one possible reason may be that environmental influences are initiating events occurring perhaps for short periods many years before loss of sight from cataract. It is important, therefore, to be able to detect the earliest changes of cataract formation so that epidemiological studies have a better chance of detecting environmental factors. Two possible indicators of early cataract are delayed growth of the lens and abnormalities of the anterior subcapsular clear zone of the lens as observed on slit-lamp microscopy. A series of patients with early lens changes was compared with control subjects in respect to these two factors. Lens thickness was measured by a simple optical method. The mean thicknesses of the lens in patients with early cortical or posterior subcapsular lens changes were significantly less than that of age matched controls. 60% of lenses with early cataract of all types were found to have a deficient or absent anterior subcapsular clear zone. Lens thickness and the appearance of the anterior subcapsular clear zone are easy to measure and observe through an undilated pupil. Although the prognostic value of the results is uncertain in individual cases owing to the rather wide scatter of results in normal eyes, such observations could be of value in comparative studies of populations.

Cataract is a major cause of blindness and ocular morbidity throughout the world, and any means of delaying or preventing its onset would have enormous social and economic benefits. If age is the sole determinant of cataract formation, there may be little we can do to realise this goal, but if environmental factors are involved there is the possibility of reducing the risk by eliminating adverse environmental conditions.

Two main observations suggest environmental factors. First, the prevalence of cataract is higher in some regions of the world and the age of onset is earlier. Weale[1] has plotted the risk of cataract against age for populations in India and South-east Asia and compared the distribution with that in European populations, and his graphs clearly show that for a given age group the risk is up to 400 times greater for the Asian populations. This does not prove an environmental influence, as genetic factors could produce the same result, but such large differences are certainly suggestive of environmental factors.

Secondly, epidemiological studies have suggested that exposure to solar radiation, particularly in the ultraviolet range, dietary deficiency, or dehydrating conditions such as recurrent severe diarrhoea may be involved.[2] Taylor,[3] for example, from surveys on Australian aborigines showed a strong association between cataract and latitude and a trend for cataracts to occur more often in areas with higher annual mean ultraviolet-B radiation levels. Other studies have attempted to link sunlight exposure by comparing populations from areas with different intensities of solar radiation. The difficulties involved in the assessment of exposure to ultraviolet radiation for varying geographic conditions have been well reviewed by Sliney.[4]

Typically such research has looked at the environment of patients with relatively advanced cataract causing severe visual disability. Cataract is thought to be multifactorial, and, if environmental factors are involved, they may be initiating events which occurred many years before its manifestation as visual loss. The latency period—the time from the initiation of disease to the time of its first clinical symptom—for cataract is poorly defined. One possible clue to this latency period is the thickness of the lens. The continuous growth of the lens throughout life was recognised as early as 1883 by Priestley Smith and has

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been amply confirmed by many later studies, notably those of Jansson,[5] Goldmann,[6] Babel *et al.*,[7] Brown,[8] and many others. There is a linear relationship between the anteroposterior thickness of the lens and age, so that the mean thickness of a normal lens in 20-year-old subjects is about 3·8 mm and that of 80-year-old subjects is about 5·2 mm. This increase in size is due to the continuous laying down of new lens fibres modified to some extent by the compaction of the older fibres, as demonstrated by the observation by Brown[8] that traumatic opacities are seen to sink into the lens at approximately twice the speed at which the lens is growing. This linear relationship between lens thickness and age makes it possible to compare the thickness of a given lens to the expected thickness for the age of the subject.

There is some evidence of racial differences in lens thickness, as Young and Leary[9] found the lenses of Eskimos to be slightly thicker than those of Caucasians. The influence of refraction on lens thickness is still uncertain, and it has been suggested that the lens of myopes is thinner and that of hypermetropes thicker than normal, but Jansson[5] and Luyckx and Delmarcelle[10] found no significant difference, and Franceschetti and Luyckx[11] and François and Goes[12] found no significant difference in lens thickness in the two eyes of anisometropic subjects.

We have just completed an epidemiological survey of 160 patients admitted for cataract extraction and an equal number of controls matched for sex and age (within one year) seen at the Department of Ophthalmology, University of Iowa.[13] A questionnaire was administered by a trained interviewer which included a detailed history of residence, occupation, lifetime sunlight exposure, acute and chronic skin reactions to sunlight, the use of glasses, sunglasses, and head covering, exposure to agricultural chemicals, and diet. In addition height and weight were recorded, and the subjects were asked for any history of alcohol abuse, diabetes, hypertension, rheumatic disease, cancers or tumours, and a history of glaucoma, retinal detachment, or other ocular conditions, and any medications such as corticosteroids, tranquilisers, antidepressants, antihypertensives, and glaucoma medication. Any family history of cataract was noted, and the refractive error, presence of pinguecula, and arcus senilis recorded. The type of cataract was classified by a modification of the classification recommended by the American Cooperative Cataract Research Group.[14]

The results of this study will be reported in detail but can be briefly summarised as follows. We could find no association with working environment or occupation, and there was no difference between the cases and controls in lifetime sunlight exposure or the use of protective devices such as glasses or sunglasses which would be expected to reduce the ocular exposure to ultraviolet light.

There were, however, three findings which were suggestive of some sunlight-senile cataract association. First, an acute skin response to sunlight was found to be significantly associated with nuclear cataract. This could, however, suggest a genetic association with light-skinned subjects or a secondary effect of sunburn rather than a direct effect on the lens. Secondly, there was a trend for fewer cataracts in men who wore head coverings. And, thirdly, there was a higher incidence of skin neoplasms in the subjects than in the controls which approached statistical significance.

There was little evidence, therefore, in this population that direct exposure of the eye to sunlight was a cause of cataract. In addition, there is one ocular condition which is almost certainly due to ultraviolet light and that is pinguecula. Pathologically the changes in pinguecula are very similar to those seen in actinic elastosis of the skin. It would be expected, therefore, that there would be a higher incidence of cataract in patients with pinguecula if cataract resulted from ultraviolet light exposure to the lens, but in this series, as in a previously published series,[15] we could find no association between pinguecula and cataract, and there was no significant difference in the incidence of pinguecula in the cataract patients and controls.

This study therefore failed to show any marked environmental factors associated with cataract in this population. Cataract is almost certainly multifactorial in origin, and in other parts of the world, the effect of age, heredity, refraction, hypertension, and glaucoma may be supplemented by dietetic deficiencies, chronic or acute intestinal disease, and environmental factors associated with the geographical area. It is possible that environmental influences initiate events occurring perhaps for short periods many years before the lens becomes opaque and the patient seeks treatment. There may be a long latent period between the onset and recognisable clinical disease, in which case it would be difficult to elicit the relevant environmental history responsible by questioning the patient when the disease is manifest.

After completion of our survey in Iowa, I realised that many of the cataract patients had had intraocular lenses implanted, and in order to estimate the power of the implant they had had preoperative ultrasound examinations. Analysis of the ultrasound measurements of lens thickness kindly provided by the Division of Ultrasonography yielded the following results.

The mean lens thickness of 87 cataractous lenses

Table 1 *Type of cataract and lens thickness*

Type of Cataract	*No.*	*Mean age*	*Mean lens thickness (SD), mm*	*Expected lens thickness, mm*	*Difference*	*p Value*
Posterior subcapsular	16	65·3	3·93±0·50	4·85	0·92	<0·001
Nuclear	23	70·0	4·45±0·67	4·97	0·52	<0·001
Cortical and subcapsular	6	62·7	4·10±0·33	4·80	0·70	<0·001
Cortical and nuclear	6	69·3	4·45±0·59	4·97	0·52	<0·046
PSC and nuclear	25	70·8	4·00±0·615	5·05	1·05	<0·001
Mature	11	67·8	3·94±0·75	4·96	1·01	<0·001

PSC=posterior subcapsular.

was 4·13 mm (SD 0·8). The mean age of the patients was 68·5 years, and according to Luyckx[16] the normal mean thickness for persons of this age would be 5 mm, which is highly significantly different ($p<0·001$). The cataracts were classified according to their slit-lamp appearance into predominantly cortical, posterior subcapsular, nuclear, or a mixture of two of these three components. When all three types of lens change were present, it was classified as a mature cataract. In Table 1 the type of cataract, the number in each group, the mean patient age, and the mean thickness of the lens are recorded and compared with the expected thickness.

There was no significant correlation between lens thickness and age in the cataract patients, and although patients with posterior subcapsular changes were younger than those with nuclear or those with posterior subcapsular and nuclear changes, there were significant differences in lens thickness (posterior subcapsular versus nuclear, $p=0·046$; posterior subcapsular versus posterior subcapsular with nuclear, $p=0·001$).

In adults the lens increases in thickness by approximately 0·2 mm every 10 years, so that the thickness of the cataractous lenses corresponds to that of the normal lens 25 to 30 years previously. Similar results have been reported.[6 7 17 18] Shibata *et al.*[19] noted that lenses with wedge-shaped opacities or posterior subcapsular opacities do not show any increase in lens thickness with age. If this failure to reach a normal thickness for age is due only to cessation of lens growth, it would imply that the cataractous lenses stopped growing 25 to 30 years before the cataract was extracted, and it could be inferred that the initiating process in cataract formation, which could be environmental, also occurred at this time.

It cannot be assumed, however, that the small size of the cataractous lens is only due to cessation of growth. Some degree of compaction of lens fibres is a normal feature[8] of lens maturation, and the changes in the cataractous lens may be the result of a combination of slower growth and greater compaction. At the moment there are no data to estimate the time scale of these processes, but it is known that the diminution of thickness is due to cortical thinning and that the nucleus is not involved. Does this occur only as a late change? The diminution of thickness of the cortex is parallelled by a diminution in the weight and volume of the lens and alterations in the structure of the proteins.[20] These authors remark that early cortical changes result in a change in refraction of the cortex which may cause the refraction of the eye to become more hypermetropic.

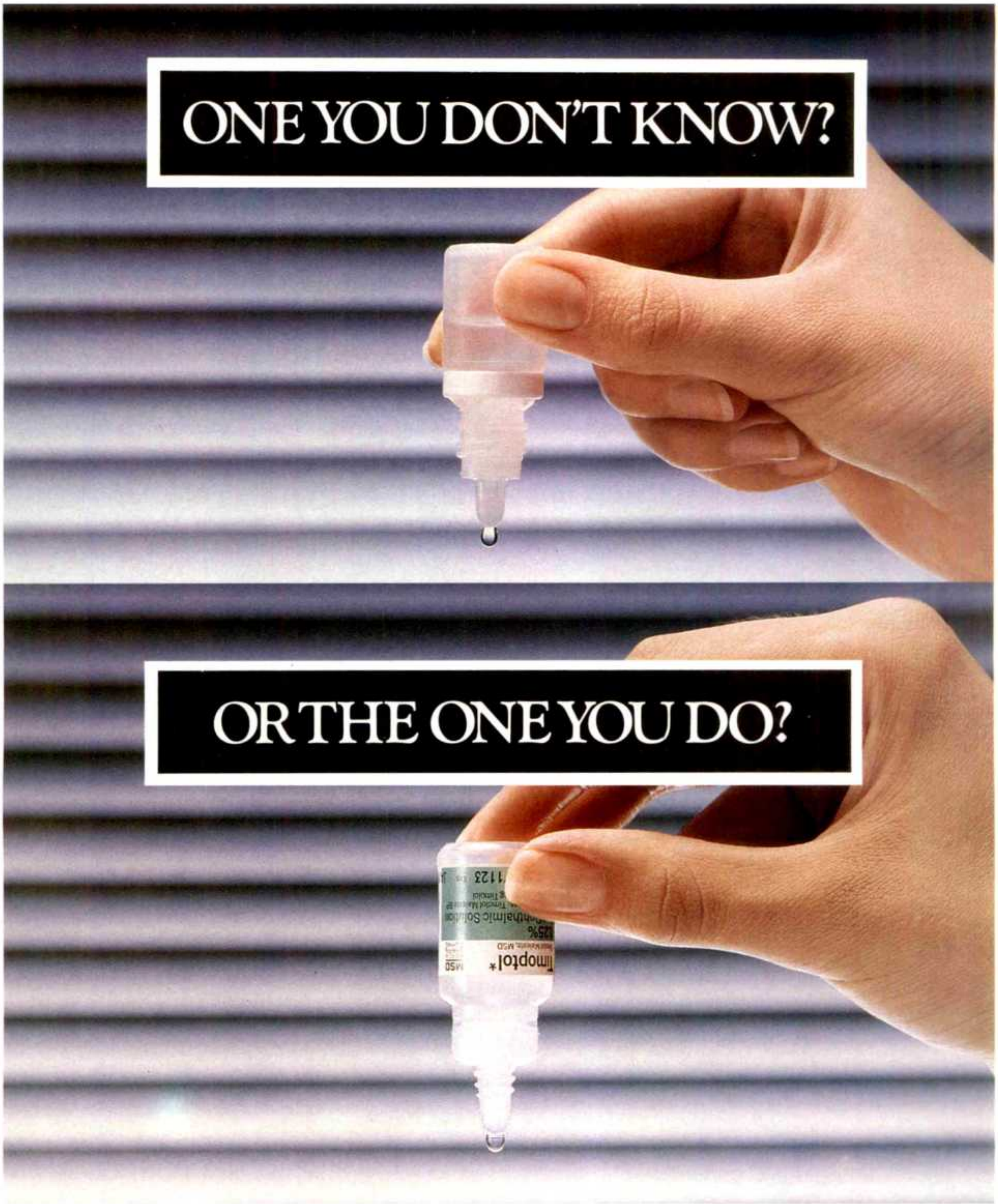
If we wish to look at aetiological factors in cataractogenesis, the results reported above indicate that it is essential to know more about the latent period of cataract, so that investigations can be aimed at the critical period when the disease starts.

Other methods of detecting early changes in the formation of cataract depend on changes in the optical quality of the lens. They include the disappearance of the anterior subcapsular clear zone, fluorescence of the lens, spectroscopic studies of the lens protein, and nuclear magnetic resonance.

Of these methods slit-lamp observation and photography are the simplest and most easily available techniques. Slit-lamp microscopy of the lens shows a number of clearly defined zones in the lens. Brown and Tripathi[21] have shown that the normal clear zone immediately beneath the lens capsule may be thinned or absent in cataract, and such lenses are usually thinner than expected for the age of the patient. A defective anterior subcapsular clear zone was almost always seen with posterior subcapsular cataract and in older patients with nuclear sclerosis. Senile cortical lens changes were not associated with changes in the anterior subcapsular clear zone. They postulate that the loss is due to a primary defect in the lens epithelium of the equatorial region which is failing to produce normal lens fibres, which also results in defective lens growth.

Examination of the subcapsular clear zone may therefore be a very useful method for detecting the early changes in the lens which lead to cataract formation. This, combined with measurement of lens thickness, could provide suitable methods of screening.

The ideal study for this purpose would be a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References

1. Zimmerman, T. J., presented at: Int. Symposium on Glaucoma, XIII Int. Co Ophthalmology, Kyoto, Japan, May 1978, 55-64.
2. Sponsel, W. E., *et al.*, *Brit. J. Ophthal.*, 1983, **67**, 220-227.
3. Sponsel, W. E., International Symposium on Glaucoma, Turin, 1986.
4. Katz, I. M., presented at: Int. Symposium on Glaucoma, XIII Int. Con Ophthalmology, Kyoto, Japan, May 1978, 29.

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Table 2 *Age distribution of all subjects*

Age	*0–9*	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*	*80–89*	*90+*	*Totals*
Clear lenses	3	10	12	10	16	16	23	10	1	0	101
Cataract	1	0	3	6	4	12	25	34	16	3	104

longitudinal study of individuals over many years. Unfortunately this is hardly practicable, but a cross-sectional study of different age groups and different stages of cataract formation should supply useful information.

The present study was designed to measure lens thickness and to note the presence or absence of the anterior subcapsular clear zone in a series of subjects with normal lenses and those with early cataract.

Material and methods

The subjects were patients attending the outpatient clinics of the Department of Ophthalmology at the University of Iowa Hospitals and Clinics in Iowa City. Anterior chamber depth and lens thickness were measured by an optical method which has been shown to correlate closely with ultrasonic measurements.[22] In this method the movement of the slit-lamp is measured when the focus of the slit is moved from the anterior surface of the cornea to the anterior surface of the lens. This apparent distance can be converted to real distance by Linstedt's formula. The sagittal thickness of the lens is measured by the movement of the slit-lamp required to focus from the anterior surface of the lens to the posterior capsule.

The anterior subcapsular clear zone was recorded as present, reduced in width, or absent, and any cataractous changes found after dilatation of the pupil were recorded. These changes were classified as cortical, nuclear, posterior subcapsular, combined cortical and nuclear, and those with posterior subcapsular changes combined with cortical or nuclear changes. The severity of the lens changes was classified as mild, moderate, or severe. In no case was the cataract interfering with vision enough to warrant cataract extraction.

Additional measurements of anterior chamber depth and lens thickness were made in some subjects with a Stortz ultrasonic A-20/20 instrument. The refractive error in spherical equivalents was also recorded for each subject.

Table 3 *Mean lens thickness (right eye) in mm*

Subjects	*Mean thickness*	*SD*	*No.*	*Probability of difference from clear lenses*
Clear lenses aged 60 and over	4·90	±0·44	34	
Cortical lens changes	4·50	±0·45	16	<0·01
Nuclear lens changes	4·84	±0·41	23	>0·1
Cortical and nuclear	4·73	±0·38	29	=0·1
PSC and other	4·52	±0·30	5	<0·05>0·01

PSC=posterior subcapsular.

Results

The age distribution of the subjects is shown in Table 2. As would be expected, there was a preponderance of older subjects with cataract.

A comparison between ultrasonic and optical measurements of lens thickness showed a good correlation ($r=0{\cdot}86$, $p<0{\cdot}001$) for clear lenses and a somewhat lower correlation for cataractous lenses ($r=0{\cdot}69$, $0{\cdot}02>p>0{\cdot}01$). This may be partly due to the smaller number of subjects with cataractous lenses measured (11) compared with 26 subjects with clear lenses, but it is possible that refractive changes in the cataractous lenses caused errors in both methods of measurement resulting in a greater scatter.

The mean lens thickness by the optical method of clear lenses in subjects aged 60 and over is compared with the mean lens thickness for different types of cataract in Table 3. Lenses with cortical opacities were significantly thinner than clear lenses in patients of similar age. Lenses with posterior subcapsular changes combined with either nuclear or cortical changes were also thinner than clear lenses but the difference was not statistically significant. Lenses with nuclear changes were very similar in mean thickness to normal lenses.

Linear regression analysis of age and lens thickness showed a highly significant relationship in subjects with clear lenses but no significant linear relationship in any of the groups of patients with lens changes. This lack of linear relationship between age and lens thickness in cataractous lenses may be partly due to the shorter age range of the patients with cataract but does also suggest that cataractous changes alter the normal growth characteristics of the lens.

There was no significant difference in the slope of the age versus thickness curve for males and females with clear lenses or between myopes and other refractive states.

Table 4 *The anterior subcapsular clear zone in normal and early cataractous lenses*

Lens	*Subcapsular clear zone*			*Total*
	Normal	*Reduced*	*Absent*	
Clear lenses	166 (85·1%)	26 (13·3%)	3 (1·5%)	195
Early cataract	50 (40·3%)	52 (41·9%)	22 (17·7%)	124

The results of assessment of the anterior subcapsular clear zone are shown in Table 4, and it will be seen that 60% of the cataractous lenses had a deficient or absent subcapsular clear zone. However, 15% of apparently normal lenses also showed some abnormality of the subcapsular clear zone, but it is impossible to say that this represents a 15% false positive rate, as it is conceivable that these lenses may be showing the earliest sign of cataractous change. The high false negative rate (40%) in the cataractous lenses is disappointing and was approximately the same for each type of lens opacity.

81% of the cataractous changes were recorded as slight and the remainder as moderate. An abnormal clear zone was present more frequently in the lenses recorded as having moderate lens changes, but the difference was not statistically significant.

Discussion

The purpose of this study was to see whether changes in lens thickness or the appearance of the anterior subcapsular clear zone could be used as an indication of early cataract formation. The results, though not as dramatic as those from patients with more advanced cataract, did show that lenses with cortical changes were significantly thinner than would be expected from the age of the patient. Lenses with nuclear changes only did not differ from normal lenses in their thickness. The difference between the thickness of clear lenses and those with cortical changes in subjects aged 60 or over was 0·42 mm, a difference which could be detected by either ultrasonic or optical methods.

Measurement of lens thickness, therefore, could be a useful parameter in population studies in association with an analysis of environmental influences. Unfortunately the scatter of lens thickness versus age is such that a difference of 0·4 mm in lens thickness is approximately equal to the standard deviation of lens thickness in normal subjects of the same age. Lens thickness cannot be used as an indicator of early cataract in individual subjects unless the difference from the expected value for age is marked.

In the hope of being able to define the limits of normal lens thickness more closely, the correlations between age and lens thickness were calculated for males and females separately, but there was no significant difference in the slope of the curve between males and females. Similarly, no significant difference could be found between myopic and non-myopic eyes.

A reduced or absent anterior subcapsular clear zone was noted much more frequently in patients with lens changes of any type than in subjects with clear lenses and abnormality of the subcapsular clear zone is strongly suggestive of early cataract (Table 4). Unfortunately, the clear zone was present in approximately 40% of patients with early cataract, so that a normal clear zone does not exclude the possibility of lens changes.

All lenses with cortical lens changes and absent or reduced subcapsular clear zone were thinner than would be expected for age (mean difference −0·66 mm). Lenses with nuclear changes only and abnormal subcapsular clear zone were little different from the expected thickness (mean difference +0·05 mm). Ten lenses with cortical and nuclear changes out of 14 were thinner than expected (mean difference −0·32 mm). Out of 14 clear lenses with an abnormal subcapsular clear zone, seven were thicker than expected and seven thinner (mean difference −0·01 mm).

In summary, lenses with cortical lens changes are thinner than would be expected for age and an abnormal subcapsular clear zone is also associated with a reduced lens thickness. Nuclear lens changes are not accompanied by thinning of the lens, but abnormalities of the anterior subcapsular clear zone do occur with this type of cataract. Lens thickness and the appearance of the anterior subcapsular clear zone are easy to measure and observe through an undilated pupil with a slit-lamp microscope, and, although their prognostic significance is uncertain in individual lenses owing to the normal variation (particularly in lens thickness), these observations could be of value in comparative studies of populations as an indication of early cataract.

This research was supported in part by an unrestricted grant from Research to Prevent Blindness.

References

1 Weale RA. The age variation of 'senile' cataract in various parts of the world. *Br J Ophthalmol* 1982; **66**: 31–4.
2 Minassian DC, Mehra V, Jones BR. Dehydrational crises from severe diarrhoea or heatstroke and risk of cataract. *Lancet* 1984; i: 751–3.
3 Taylor HR. The environment and the lens. *Br J Ophthalmol* 1980; **64**: 303–10.
4 Sliney DH. Physical factors in cataractogenesis: ambient ultraviolet radiation and temperature. *Invest Ophthalmol Vis Sci* 1986; **27**: 781–90.

5 Jansson F. Measurements of intraocular distances by ultrasound. *Acta Ophthalmol (Kbh)* 1963; **74** (suppl); 1–151.

6 Goldmann H. Senile changes of the lens and vitreous. *Am J Ophthalmol* 1964; **57**: 1–13.

7 Babel J, Psilas K, Hin W. Measures échographiques de l'épaisseur du cristallin dans les cataracts unilateral. In: Boch J, Ossoinig K, eds. *Ultrasonographia medica.* Vienna: Wiener Medizinische Akademie, 1971: 547–55.

8 Brown N. Dating the onset of cataract. *Trans Ophthalmol Soc UK* 1976; **96**: 18–23.

9 Young FA, Leary GA. Comparative oculometry of Caucasians, Eskimos and chimpanzees. In: Boch J, Ossoinig K, eds. *Ultrasonographia medica.* Vienna: Wiener Medizinische Akademie, 1971: 595–612.

10 Luychx J, Delmarcelle Y. Biometrie du globe oculaire en fonction de l'âge et de la réfraction chez l'enfant. In: Massin M, Ponjol J, eds. *Diagnostica Ultrasonia in Ophthalmologia.* Centre Nat Ophtal Quinze-Vingts, Paris: 1973: 269–75.

11 Franceschetti A, Luyckx J. Etude de l'effect emmetropisant du cristallin par la méthode d'échographie ultrasonique. *Ann Oculist (Paris)* 1967; **200**: 177–90.

12 François J, Goes F. Comparative study of ultrasonic biometry of emmetropes and myopes with special regard to the heredity of myopia. In: Griter K, Kenney A, Sarin L, Meyer D, eds. *Ophthalmic ultrasound.* St Louis: Mosby, 1969: 165–80.

13 Dolezal J. Factors associated with senile cataract. University of Iowa, 1986: Ph D thesis.

14 Chylack LT Jr, Lee MR, Tung WH, Cheng HM. Classification of human senile cataractous change by the American Cooperative Cataract Research Group (CCRG) method 1. Instrumentation and techniques. *Invest Ophthalmol Vis Sci* 1983; **24**: 424–31.

15 Perkins ES. The association between pinguecula, sunlight and cataract. *Ophthalmic Res* 1985; **17**: 325–30.

16 Luyckx J. Contribution de l'ultrasonographic A à l'étude du glaucome à angle fermé. In: Bock J, Ossoinig K, eds. *Ultrasonographia Medica.* Vienna: Wiener Medizinische Akademie, 1971: 573–7.

17 Delmarcelle Y, Luyckx J. Influence de la cataracte sénile sur l'épaisseur du cristallin et la profondeur de la chambre antérieure. *Bull Soc Belge Ophtalmol* 1970; **155**: 465–73.

18 Brown H, Hungerford J. The influence of the size of the lens in ocular disease. *Trans Ophthalmol Soc UK* 1982; **102**: 359–63.

19 Shibata T, Hockwin O, Weigelin E, Kleifeld O, Dragomirescu V. Biometrie der Linse in Abhangigkeit von Lebensalter und von der Kataractmorphologie. Answertung von Scheimpflug Photos des vorderen Augenabschnittes. *Klin Monatsbl Augenheilkd* 1984; **185**: 35–42.

20 Lahm D, Lee LK, Bettelheim FA. Age dependence of freezable and nonfreezable water content of normal human lenses. *Invest Ophthalmol Vis Sci* 1985; **26**: 1162–5.

21 Brown N, Tripathi R. The loss of the anterior subcapsular clear zone of the lens. Prognostic significance in cataract formation. *Trans Ophthalmol Soc UK* 1974; **94**: 29–44.

22 Perkins ES. Depth measurement with the slit-lamp microscope. *Br J Ophthalmol* 1988; **72**: 344–7.

Accepted for publication 5 March 1987.

British Journal of Ophthalmology, 1988, **72**, 354–360

Experimental epikeratophakia using tissue lathed at room temperature

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SUMMARY This report presents for the first time the results of carrying out epikeratophakia with tissue lathed at room temperature. Using an experimental model of epikeratophakia in the rabbit, we evaluated tissue handling techniques for the preparation of donor lenticules. Details of the technique are described and the in-vivo and histopathological findings reported.

Epikeratophakia is a keratorefractive procedure developed by Kaufman and McDonald.[1] The operation uses lathed donor corneal tissue which is sutured on to the de-epithelialised surface of a recipient eye to change the anterior corneal curvature. The host epithelium grows back over the top of the donor tissue, so that it becomes permanently incorporated as a 'living contact lens'. The shape of the grafted tissue can be modified to correct virtually any degree of hypermetropia or myopia (Fig. 1).

To produce the lenticule for epikeratophakia donor corneal tissue is frozen on to a cryolathe and cut into shape while in the frozen state. The lenticule is then thawed and removed from the cryolathe, and may subsequently be lyophilised (freeze dried), which renders it stable at room temperature. Lyophilisation allows corneal tissue to be lathed to an individual patient's specification at a specialist centre and subsequently made available to a surgeon at a separate centre where the refractive surgery is to be performed.

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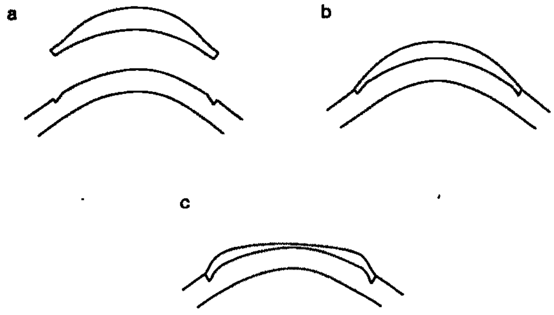


Fig. 1 *Epikeratophakia.* (a) *Lathed donor tissue and recipient cornea with groove cut to receive the edge of the graft.* (b) *Hypermetropic epikeratophakia graft.* (c) *Myopic epikeratophakia graft.*

In 1982 Maguen and Nesburn[2] reported a new technique of lathing corneal tissue at room temperature without a cryolathe. For this technique corneas are lyophilised with a sucrose solution which makes them adherent to a special plastic base. The dried cornea can then be lathed at room temperature on an ordinary contact lens manufacturing lathe. Maguen and colleagues reported the results of performing the refractive procedure of keratophakia in cats, using tissue processed in this way.[3] However, there have been no reported results of epikeratophakia surgery on corneas lathed at room temperature. Commercially prepared tissue for epikeratophakia is now generally lyophilised after cryolathing to stabilise it for transport. If the tissue is to be lyophilised anyway, it could equally be lyophilised before lathing and then lathed at room temperature. Lathing in this way has the advantage of avoiding the thermally induced dimensional changes encountered on the cryolathe, as well as giving clear visibility of the tissue at all stages without the obscuration caused by the build up of ice deposits.

This study set out to simplify Maguen and colleagues' method of lathing at room temperature,[3] and to evaluate techniques for producing lathed tissue for epikeratophakia. A rabbit model was chosen because of the ease of handling this experimental animal.

Material and methods

DONOR EYES

Donor rabbit eyes were enucleated at the time of death and stored for up to 24 hours at 4°C. This initial storage induces some degree of epithelial cell swelling but allows the epithelium to be removed with less trauma. Corneal buttons were prepared by stripping the epithelium with a blunt scalpel and excising the whole cornea. Descemet's membrane and the endothelium were also completely stripped with fine forceps. We found this helped avoid distortion of the tissue during drying. An 8 mm button was punched from the stroma on a block. The button was placed in freeze drying solution for 30 minutes and either preserved in liquid nitrogen for an intermediate period or used straight away for further processing.

FREEZE DRYING SOLUTION

This sucrose-containing solution makes the corneal buttons adherent to the polymethylmethacrylate (PMMA) bases when they are dried. The solution was prepared by dissolving sucrose, 216 g/l, and dimethylsulphoxide (DMSO), 81 ml/litre, in dextran 70 in 0·9% normal saline.

PMMA BASES

A single PMMA base was used for both the lyophilisation and lathing processes. The base was made from a cylindrical block of PMMA 13 mm in diameter and 1·2 mm high, with a recess cut in the top of the cylinder of 8 mm chord width and an 8 mm radius cut into which the donor button was placed. The base and button were then placed in a desiccation jar at 4°C for 14 hours for preliminary desiccation prior to lyophilisation.

LYOPHILISATION

Rapid freezing of the button on the base was achieved by plunging it into liquid nitrogen before it was placed on to the precooled platform of the lyophiliser (Edwards-Pearse Tissue Dryer Model EPD3). Lyophilisation was carried out with a platform temperature of −30°C, and at 10 mTorr pressure for 24 hours. The lyophilised tissue was then ready for lathing.

LATHING

Prior to lathing, the corneal thickness was determined with a contact lens measuring gauge. To mount the PMMA base on the lathe; dental wax with a melting point of 65°C was applied to the surface of a heated brass mounting chuck. The PMMA base was then applied and centred on the revolving chuck as the wax hardened. The brass chuck was mounted in the collet of a standard Nissel contact lens manufacturing lathe. Lathing was performed at 5000 rpm with a standard diamond cutting tool of 0·3 mm diameter. Optic zone cuts of various radii were made while maintaining a constant optic zone size and wing width.

SURGICAL SERIES

Adult female New Zealand White rabbits were kept at 21°C and given food (diet FD1 SDS, Witham Essex) and water ad libitum. The animals underwent epikeratophakia surgery to one eye only, the other eye serving as a control. Surgical procedures were carried out under general anaesthesia, and full postoperative care was given, including analgesia as required. Each animal underwent a preliminary operation of excision of the nictitating membrane in the eye to be grafted. Epikeratophakia surgery was carried out one to four weeks later. Sutures were removed at 10 days after grafting.

ANAESTHESIA

For excision of nictitating membrane, and removal of sutures, the rabbits were given midazolam (Hypnovel) 1 ml intravenously followed by titrated fentanyl 0·2 mg/ml with fluanisone 10 mg/ml (Hypnorm) about 0·3 ml per kg, with topical cocaine, and oxygen by mask. Recovery was aided by naloxone (Narcan) 0·5 ml intramuscularly.

For the epikeratophakia surgery anaesthesia was maintained with oxygen 1 litre/min, nitrous oxide 2 litres/min, and 2%–4% halothane by mask, with monitoring of respiration, electrocardiogram (ECG), and core temperature. Postoperatively supplementary buprenorphine (Temgesic) 0·05 mg/kg subcutaneously was given if necessary, though the majority of animals made a rapid recovery and did not require further analgesia.

NICTITATING MEMBRANE

Following epikeratophakia surgery, continuous wear of a bandage soft contact lens ensured rapid re-epithelialisation of the graft. Initially it was found that the rabbit's nictitating membrane would repeatedly dislodge a contact lens, with resultant complications. However, surgical removal of the nictitating membrane virtually eliminated the problem of contact lens loss, as well as greatly facilitating ocular examination and the insertion or removal of the bandage contact lens. Removal of the nictitating membrane did not appear to have any effect on the eye, and there were no complications from this procedure.

EPIKERATOPHAKIA SURGERY

This was carried out in a manner similar to that advocated by McDonald and Kaufman for human epikeratophakia surgery[4] with only minor modification to suit the animal model. The eye was stabilised with superior and inferior rectus sutures. A 7·5 mm diameter Hessburg-Barron vacuum trephine was centred on the cornea and a partial thickness cut made by turning the screw-threaded trephine blade three-quarter turns. The epithelium was stripped only within the area delimited by the trephine cut, with a blunt curved scalpel blade. A groove was formed on the inner side of the trephine cut with curved Vannas scissors. The stroma was split peripherally for approximately 1 mm at the base of the groove. The lenticule was applied after being rehydrated in McCarey-Kaufman (MK) medium. Four interrupted sutures were used to stabilise the lenticule, while a single continuous anti-torque 10′0′ Dermalon suture was applied. The interrupted sutures were removed prior to tying the continuous suture. Finally topical chloramphenicol and subconjunctival methyl prednisolone (Depo-Medrone) 0·04 ml were given and a custom made bicurve Ledasoft 80% bandage soft contact lens (rad: 6·00—diam: 7·50, 2nd. rad: 8·00—overall diam: 15·00) fitted.

POSTOPERATIVE MANAGEMENT

The animals received no routine postoperative treatment, but signs of postoperative uveitis if present were treated with topical betamethasone/neomycin (Betnesol N) ointment, though this was rarely required. Sutures were removed at 10 days postoperatively, and bandage contact lens wear was discontinued two to three weeks postoperatively depending on the state of the epithelium.

EVALUATION

It was found that the rabbit support designed by Maurice and Singh[5] allowed easy access to perform slit-lamp biomicroscopy and keratometry on the unsedated animal without any difficulty. Keratometry was performed preoperatively, two weeks postoperatively, and at intervals thereafter. Anterior segment photography was carried out weekly.

HISTOPATHOLOGY

Animals were killed by an overdose of sodium pentobarbital. The eyes were immediately enucleated, and for light microscopic examination the corneas were excised and fixed in 10% formalin. Glycol methacrylate resin was used for embedding. The components of this resin system are water miscible, prior to polymerisation, so avoiding the tissue distortion and shrinkage associated with dehydration using alcohol. After being washed the corneas were lightly stained with acid fuchsin to facilitate orientation of the cornea in the embedding medium. The corneas were taken up through graded dilutions of the resin mix, which was then polymerised with N-N dimethylaniline. Sections of 4 μm were cut and stained with haematoxylin and eosin.

For electron microscopic examination the eyes were fixed by immersion in Karnovsky's EM fixative for at least six hours at 4°C. Selected areas of cornea were washed in two changes of cacodylate buffer, dehydrated in graded alcohols, and embedded in epoxy resin (E mix).

Semithin sections of each block were cut on a Reichart OMU3 ultramicrotome at approximately 0·5 μm with glass knives and stained with toluidine blue for light microscopic examination.

Ultrathin sections of selected blocks were mounted on copper grids, stained with lead citrate and uranyl acetate, and examined with a Jeol 100CX Temscan electron microscope.

Results

In an initial series of 15 rabbits changes were made in various aspects of the tissue handling, operative techniques, and management to optimise the procedure. Some animals suffered postoperative weight loss. The dose of Depo-Medrone turned out to be critical, as in the initial doses used it had deleterious effects, producing a diabetic type syndrome with raised blood sugars and weight loss. There were no adverse effects on behaviour or appetite, and the condition could be alleviated by occasional injections of insulin (1–2 units soluble depending on glucose levels).

Although our lyophilised tissue always appeared transparent when dry, it was found on using some solutions that varying degrees of opacification became apparent when the tissue was rehydrated.

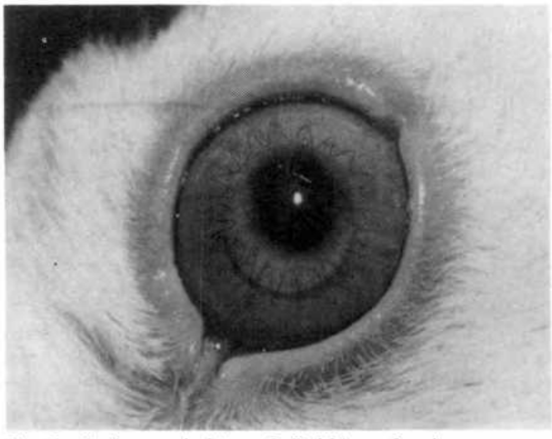


Fig. 2 *Epikeratophakia graft. Rabbit eye five days postoperatively showing continuous suture and clear graft.*

Mild stromal haziness in such grafted tissue usually cleared in the first few weeks, but some more cloudy grafts never cleared and suffered from epithelial instability and subsequent superficial stromal melting.

With refinement of the tissue handling and change in the adhesive solution it was subsequently possible to prepare consistently clear lenticules which remained clear on rehydration and on which the epithelium rapidly stabilised (Fig. 2). Re-epithelialisation was usually complete by four or five days postoperatively. Some degree of superficial punctate epitheliopathy usually persisted until a few days after suture removal. Epithelial stability did not appear to be affected by the degree of corneal steepening or flattening induced by the graft. No case of corneal epithelial ingrowth or of epithelial islands on the graft-host interface was encountered.

REFRACTIVE RESULTS

In a series of nine rabbits given hypermetropic epikeratophakia grafts up to +17 dioptres of keratometric change at the corneal plane was obtained. The lenticules used were cut to arbitrary radii and thickness, and no attempt was made to obtain a specific dioptric connection. Most of the experimental animals were culled less than one month postoperatively. The graphs in Fig. 3 show the keratometric change in three rabbits that were followed up to determine refractive stability.

Figs. 3a and 3b are of animals given hypermetropic epikeratophakia and Fig. 3c myopic epikeratophakia. The graphs show average keratometry, the bars representing the individual vertical and horizontal keratometric readings. Keratometric change in the contralateral unoperated eye is also shown. A slight degree of corneal flattening as the animal matured was evident in all three animals. These preliminary results indicate that the lenticule reached a near stable state by one month postoperatively. Initial efforts in this research were to obtain consistently clear corneas, without particular emphasis on the refractive side. Having developed this model we are using it to evaluate the lathing parameters in more depth. The predictability of refractive correction obtained with lenticules made by this technique has yet to be determined. Maguen *et al.*[3] achieved good predictability lathing for keratophakia at room temperature, and it is hoped to be able to demonstrate similar results with epikeratophakia.

HISTOPATHOLOGY

We carried out histopathological examination of specimens from five days to four months postoperatively. We found that, although the epithelial cover of the graft was macroscopically complete by about five days, the epithelial sheet was composed only of a monolayer of cells, and this was reflected clinically by the presence of fine punctate staining with fluorescein.

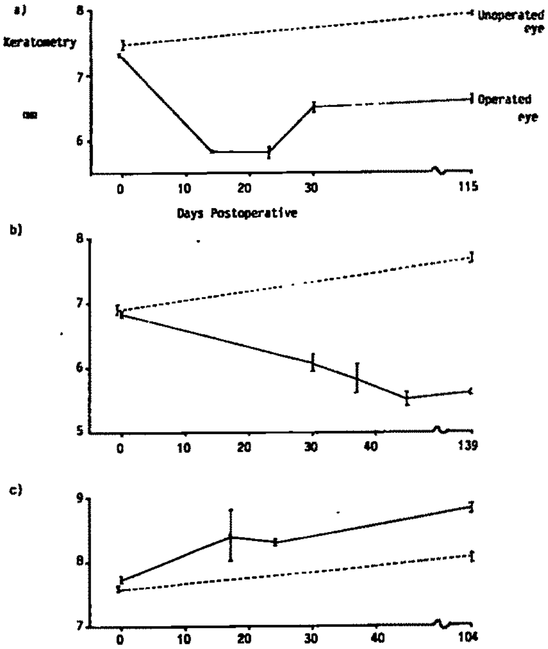


Fig. 3 *Keratometric results. Graphs showing vertical and horizontal keratometric readings (vertical bars). Continuous lines show operated eye, dotted lines unoperated eye of same animal.* (a) *and* (b) *Hypermetropic epikeratophakia.* (c) *Myopic Epikeratophakia.*

Within a short period of time the epithelial layer stabilised and thickened, attaining near normal thickness and morphology at two to three weeks postoperatively. In contrast the repopulation of the graft stroma was much slower and the rate of repopulation more variable. After grafting, the donor keratocyte cellular debris was quickly dispersed, and the homogeneous appearance of the lenticule was in sharp contrast to the underlying cellular host stroma.

Fig. 4 shows the light microscopic appearance through the centre of a hypermetropic epikeratophakia graft at six weeks postoperatively. The epithelial layer is seen to be of normal thickness and appearance. The lenticule in this section accounts for approximately one-third of the total stromal thickness. The graft-host junction is clearly apparent, not only because of the contrasting appearance of the lenticule stroma but also because the graft-host interface was highlighted by a degree of cellular proliferation. Only scanty keratocytes were seen in this central part of the lenticule. The repopulation of the tissue with keratocytes was usually apparent

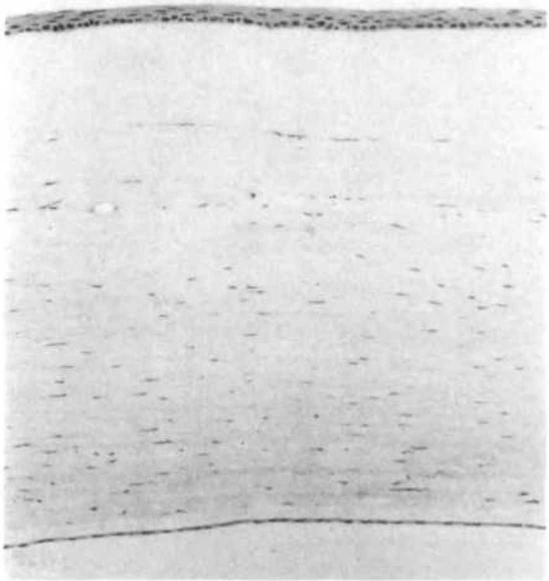


Fig. 4 *Epikeratophakia graft section. Low power. Light micrograph showing well epithelialised graft with scanty keratocyte repopulation (Six weeks postoperative). Haematoxylin and eosin.*

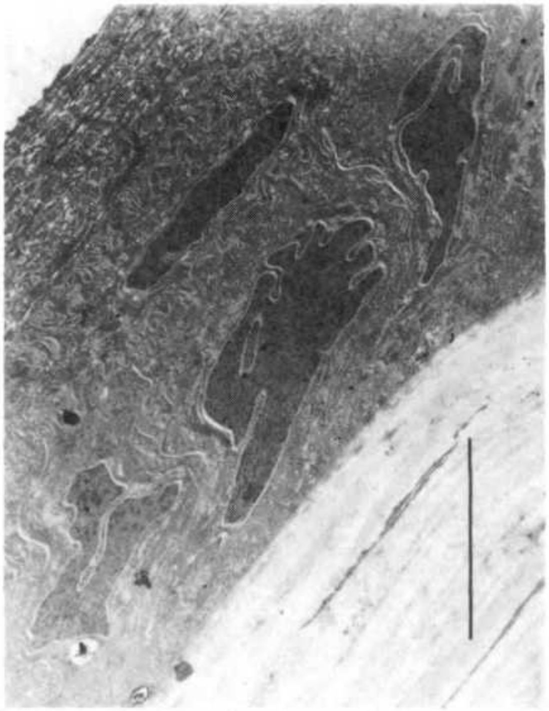


Fig. 5 *TEM graft epithelium. Section of epithelium over centre of graft four months postoperatively, showing normal appearance of cellular layer. Bar= 5µm).*

within two or three weeks postoperatively and was seen first at the periphery of the lenticule.

It appears that the keratocytes can only readily migrate in a transverse direction between the lamellae of the lenticule. The configuration of the tissue lamellae at the graft/host interface may determine the ease with which cells can migrate into the lenticule.[6] It has been found clinically that the bonding of the lenticular stroma to that of the host is largely confined to the area of the annular keratectomy. If the wound is divided in this region, the lenticule will lift off the host in the central optic zone area with ease. This lack of scarring or bonding in the optic zone was sometimes apparent histologically by the presence of small areas of artefactual separation between the layers brought about during preparation of the section. In the early postoperative phase cells could occasionally be seen lying on the graft host interface, but once the graft tissue became repopulated with keratocytes the junction could often be difficult or impossible to detect.

Fig. 5 is a transmission electron micrograph of the epithelium overlying the centre of an epikeratophakia lenticule at four months postoperatively. The cells can be seen to be of normal appearance. Fig. 6 shows the appearance of the underlying graft stroma in the same animal. The keratocyte population is indistinguishable from that of the underlying host stroma, and the normal structure of the extracellular collagen matrix is demonstrated.

Discussion

TISSUE PREPARATION

Maguen and colleagues' freeze drying solution consisted of glucose, DMSO, and kiton green dissolved in fresh frozen plasma. For this experimental work a number of changes were made. Plasma was not used, with a view to facilitating transfer of the technique to human use, and our solution was based on Dextran 70 in 0·9% normal saline. As the corneal tissue is clearly visible at all stages of the processing, the kiton green dye was not necessary, so this was eliminated. Since all keratocytes are killed during the lyophilisation process, the cryoprotective effect of DMSO on the corneal cells was irrelevant. However, in experi-

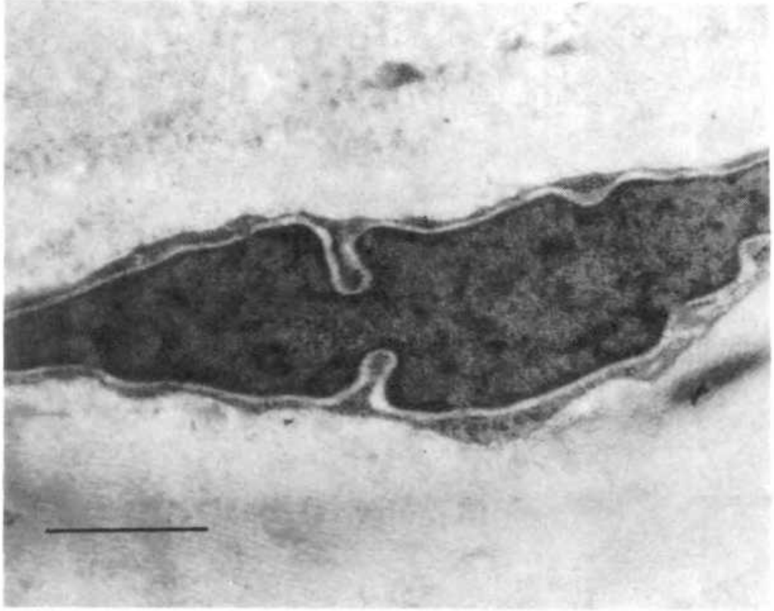


Fig. 6 *TEM graft stroma. Section of graft stroma in centre of lenticule four months postoperatively, showing normal appearance of keratocytes and collagen lamellae. Bar=1 µm.*

ments with different solutions DMSO did appear to exert some beneficial effect on stromal clarity for corneas undergoing the freezing process, so DMSO was retained in the modified solution. Sucrose allows adhesion of the dried cornea to the PMMA base for lathing, and a concentration equivalent to Maguen and colleagues' double strength solution was used.

Maguen and colleagues lyophilised the corneal button on a PMMA base which had a cap fitted to it. The dried button was then removed from this base and made adherent to a second base with a biological adhesive solution which was essentially a concentrated form of the freeze drying solution. We used a single PMMA base for both the lyophilisation and lathing. This simplified the procedure and avoided the difficulty of accurately positioning the lenticule on the second base after lyophilisation.

If the corneal button is placed on the PMMA base and allowed to dry in a desiccation jar at 4°C for 12 hours, it becomes adherent to the base. If the drying is allowed to continue for a further 24 or 48 hours, the corneal tissue hardens sufficiently to allow lathing to be carried out without the necessity for lyophilisation. However, to ensure perfect drying and to stabilise the corneal condition for storage at room temperature, lyophilisation was carried out after the initial desiccation period.

There are many factors in the various stages of donor tissue preparation, intermediate storage, lyophilisation, and lathing that can affect the quality of the lenticules. A marked variability in the tissue clarity on rehydration was initially encountered. This variability was not, however, apparent prior to rehydration, the tissue remaining uniformly clear throughout the processing. By variation of the tissue handling technique with careful control over as many variables as possible lenticules of excellent clarity were subsequently produced.

It is interesting to note that human corneal tissue processed in the same way for the purpose of non-clinical experimental evaluation showed similar, although much less pronounced, variation in clarity. It would seem possible that the rabbit cornea, because it has less structural resilience, may thus be a more sensitive marker to test the effects of variation in tissue handling. While the technique we have set out here can be used to produce lenticules of consistent clarity, further work is needed to identify those factors which require critical control and those to which more latitude can be given.

CONCLUSION

Lenticules for epikeratophakia have been produced by a simplified system of lathing at room temperature. A rabbit model was used to evaluate tissue handing techniques, and the production of consistently clear lenticules was achieved. Using this model we achieved significant refractive change, but further work is needed to quantify lathing parameters and their refractive effects.

We thank Mr A Irving of D Thomas Contact Lenses for technical assistance with lathing, Dr C Bouch, Mrs L Palmer, and Mr T Simms for the histopathology, Mr M Eagles, Mr M Allen, and Mr A

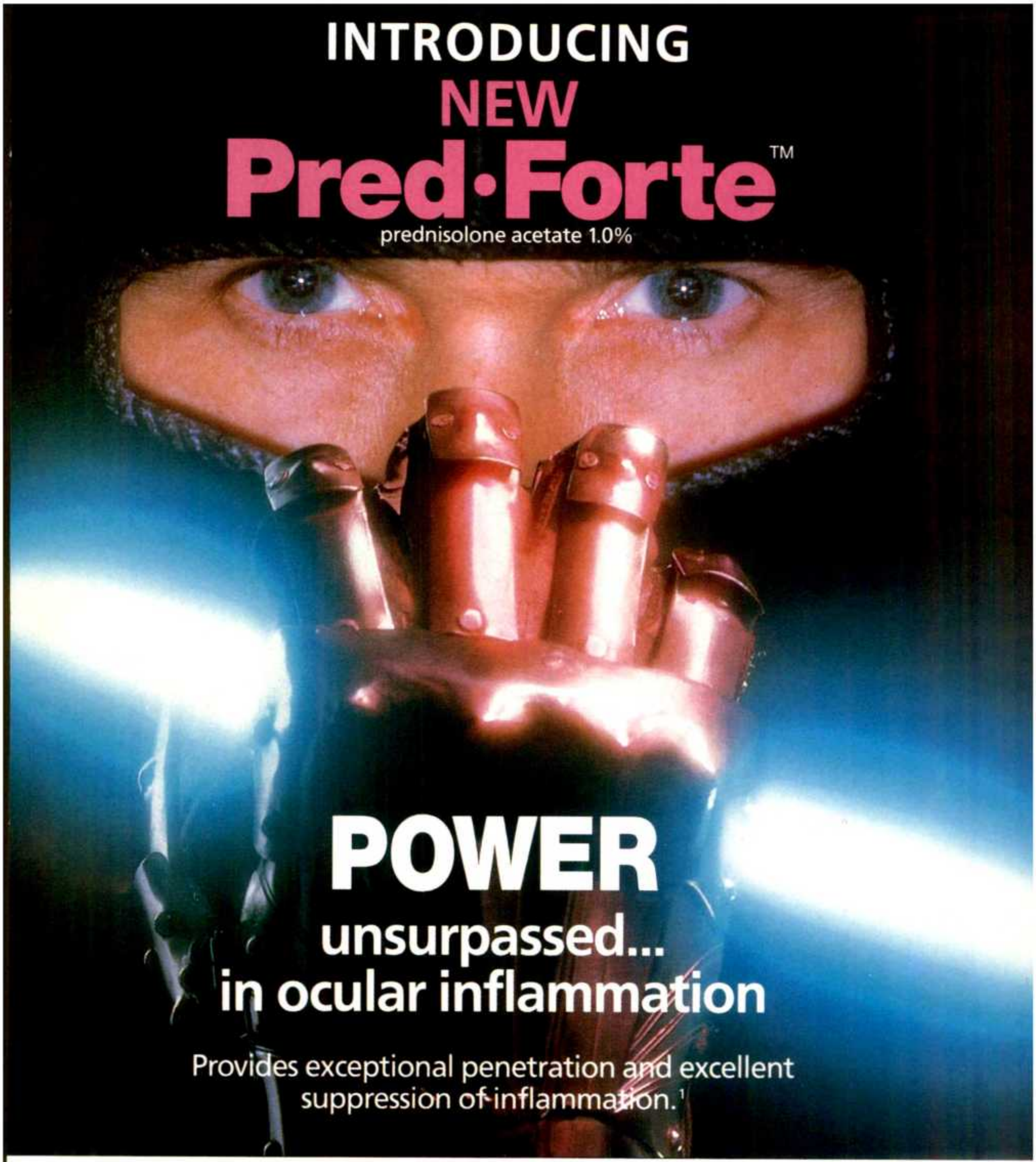
Lawrence for technical assistance with cyropreservation and lyophilisation, Mr P Husken for his technical assistance with the rabbits, and my wife for the preparation of the manuscript.

This work was supported by a Locally Organised Research Grant from the Trent Regional Health Authority.

References

1 Kaufman HE, McDonald MB. Refractive surgery for aphakia and myopia. *Trans Ophthalmol Soc UK* 1985; **104:** 43–7.
2 Maguen E, Nesburn AB. A new technique for lathing lyophilised cornea for refractive keratoplasty. *Arch Ophthalmol* 1982; **100:** 119–21.
3 Maguen E, Pinhas S, Verity SM, Nesburn AB. Keratophakia with lyophilised cornea lathed at room temperature. New techniques and experimental results. *Ophthalmic Surg* 1983; **14:** 759–62.
4 McDonald MB, Kaufman HE. Epikeratophakia for aphakia, myopia and keratoconus in the adult patient. In: Sanders DR, Hofmann RF, Salz JJ, eds. *Refractive corneal surgery.* New Jersey: Slack, 1986: 430–6.
5 Maurice DM, Singh T. An improved method for restraining rabbits for examination of the eye. *Invest Ophthalmol Vis Sci* 1984; **25:** 1220–1.
6 Yamaguchi T, Koenig SB, Kimura T, Werblin TP, McDonald MB, Kaufman HE. Histological study of epikeratophakia in primates. *Ophthalmic Surg* 1984; **15:** 230–5.

Accepted for publication 5 March 1987.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British Journal of Ophthalmology, 1988, 72, 361–362

Treatment of senile entropion with botulinum toxin

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SUMMARY Botulinum toxin was used to treat senile entropion in 12 patients by injection into the preseptal orbicularis muscle of the lower lids. It produced relief of symptoms in 10 patients but this was transient, lasting for an average of 14·8 weeks before orbicularis function returned. The technique is simple and easy to perform, and may be useful in selected patients, but surgery offers a more permanent result.

Senile or spastic entropion is a common cause of ocular discomfort and disability in the elderly. Aging changes cause tissue laxity in the lid retractors, canthal tendons, and tarsal plate of the lower eyelid. Involutional loss of orbital content also plays a part in increasing the effective lid laxity.[1] There is an upward movement of the preseptal and pretarsal parts of the orbicularis muscle, which then act to roll the upper lash-bearing edge of the eyelid against the globe. If this is neglected, corneal complications may ensue.

A variety of surgical procedures have been devised over the years to correct the inturned lower lid, but after most of these the condition may recur.[1-6] The techniques consist of one or more permutations—from shortening the lower lid retractors, shortening the horizontal length of the tarsus, forming a barrier to upward movement of the preseptal orbicularis muscle, or tightening and tethering this muscle at the lower border of the tarsal plate. A further therapeutic possibility would be to prevent the inward rolling of the lid by weakening that part of the orbicularis muscle responsible—the preseptal part and probably the upper pretarsal part near the lash margin.

The safety of localised injections of botulinum toxin into the extraocular and periorbital muscles has been demonstrated recently in the treatment of strabismus and idiopathic blepharospasm.[7 8] The toxin blocks the release of acetylcholine at myoneural junctions, and the resulting local flaccid paralysis recovers only with the growth of new end plates from the peripheral motor neurone axons, which takes many weeks. An injection of botulinum toxin into the orbicularis muscle of the lower eyelid would be expected to stop the upriding and inverting effect, though not affecting the associated tarsal and lid retractor laxity.

We report the results of treatment with botulinum toxin in 12 patients with senile entropion.

Patients and methods

Twelve patients with senile entropion accepted treatment by injection after explanation of the effect of the toxin and the alternative treatment methods available. Six men and six women were treated; their mean age was 70·7 years (range 54–86). Nine patients had had the entropion for six months or less, but three had a much longer history, and two of these had had previous entropion surgery, twice in one case. Five patients had bilateral entropion, seven unilateral. The toxin was obtained from Dr A B Scott, of the Pacific Medical Center, San Francisco, and its use required a detailed consent form under the auspices of the United States Food and Drug Administration, the Department of Health and Social Security, and St Thomas's Hospital Ethical Committee. The toxin was supplied in ampoules containing 140 units (equivalent to 50 nanograms) of freeze-dried botulinum toxin A. This was reconstituted and diluted with sterile normal saline for injection to provide 12·5 units in 0·5 ml. This was injected subcutaneously over the orbicularis muscle 3–4 mm below the lashes, along the length of the lower lid. The patients were re-examined within 48 hours, again after one week, and at lengthening intervals thereafter. The success of the treatment was assessed by the presence or absence of spontaneous entropion and symptoms. Residual or returning inverting power was assessed by observing the tendency for the lid to

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turn in on forcible voluntary lid closure with the upper lid held open.

Results

There was no apparent latent period before the entropion was relieved, because the volume of the injection at this site tended to pull the lashes from the globe mechanically. In 11 patients (including the two who had had previous surgery) the relief was immediate and sustained. In one patient the injection had failed at the first subsequent visit, probably because it was placed too close to the lid margin so that the preseptal orbicularis was not paralysed, and surgical treatment was arranged. One patient was lost to follow-up. The mean duration of relief from the entropion for the remaining 10 patients was 14·8 weeks (range 6–28 weeks). Four patients had second injections, and follow-up was long enough to observe an increased duration of effect in two of these, the period of symptomatic relief being extended from 14 weeks and 12 weeks after the first injection to 36 and 22 weeks respectively.

At this stage both patients had a surgical correction. The length of time to recurrence varied widely, but this reflects the return of symptoms rather than the return of orbicularis function. By using the forced lid closure test already described the return of orbicularis function could be seen to precede symptomatic relapse, which was very variable, as many patients seem able to tolerate minor degrees of entropion without complaint.

The only side effect observed was a temporary facial droop with slight flattening of the cheek reported by one patient and observed in another. Despite the precise localisation of the injection, our impression was that the toxin spread to weaken the pretarsal and preseptal parts of the orbicularis muscle inferiorly. No diplopia or extraocular muscle weakness occurred in any of these patients. Ectropion did not occur. There were no systemic effects, but some patients found the injection painful.

Discussion

This small study demonstrated the effective but temporary relief of senile entropion by obliterating the action of the orbicularis muscle at the lower lid. This is despite a previous study in which paralysing the orbicularis with an injection of local anaesthetic was ineffective in relieving involutional entropion.[9] Botulinum toxin appears to be effective for about three months and may be repeated. There may be a suggestion that a second injection is effective for longer than the first, possibly owing to some subsequent muscle atrophy or persisting disruption of muscular innervation, though this has not been the experience with the treatment of essential blepharospasm.

Surgical treatment of senile entropion is more reliable and persistent and must remain the treatment of choice. Botulinum toxin is, however, easy to use and is very safe at these minute dosages. It has the advantage that it can be given at the initial consultation and may have a role to play for patients where there is a long waiting list for surgery, or in those unable or unwilling to have an operation, and in the few cases where transient relief of the entropion is all that is required. If the pharmacological action could be potentiated, it would be more effective, and it is possible that repeated injections would induce more muscular atrophy with longer periods being required between injections.

Botulinum toxin is at present available only to authorised investigators, but it is likely to become more generally available for a variety of uses in the near future.

References

1 Collin JRO, Rathbun JE. Involutional entropion, a review with evaluation of a procedure. *Arch Ophthalmol* 1978; **96:** 1058–64.
2 Dryden RM, Leibsohn J, Wobig J. Senile entropion: pathogenesis and treatment. *Arch Ophthalmol* 1978; **96:** 1883–5.
3 Hargiss JL. Inferior aponeurosis tucking revisited. *Ophthalmology* 1980; **87:** 1001–4.
4 Quickert MH, Rathbun JE. Suture repair of entropion. *Arch Ophthalmol* 1971; **85:** 304–5.
5 Wies FA. Spastic entropion. *Ophthalmology* 1955; **59:** 503–10.
6 Wheeler JM. Spastic entropion correction by orbicularis transplantation. *Am J Ophthalmol* 1939; **22:** 477–83.
7 Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 1980; **87:** 1044–7.
8 Elston JS, Russell RWR. Effect of treatment with botulinum toxin on neurogenic blepharospasm. *Br Med J* 1985; **290:** 1857–9.
9 Fox SA. The etiology of senile entropion. *Am J Ophthalmol* 1959; **48:** 607–11.

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British Journal of Ophthalmology, 1988, **72**, 363–367

Experimental studies on the pathogenesis of retinopathy of prematurity

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SUMMARY The angiogenic activity of various parts of the retina in kittens with oxygen-induced retinopathy has been studied by the use of a corneal micropocket technique and chorioallantoic assay. The results indicate that in retinopathy of prematurity the most important role in the pathogenesis of fibrovascular proliferation is played by the so-called primary avascular retina, that is, that part of the retina which has not yet been vascularised during ontogenesis.

Retinopathy of prematurity is one of the proliferative retinopathies, and is a significant cause of blindness in children. The primary pathological change in this disease is peripheral fibrovascular proliferation of the retina. It is thought that this proliferation is caused by diffusable biochemical substances which possess angiogenic properties. These substances are presumably liberated in the ischaemic and, as a result, hypoxic retina.[1] In most proliferative retinopathies the development of neovascularisation is preceded by the appearance of retinal ischaemic areas (capillary non-perfusion areas) which can be detected by fluorescein angiography. In retinopathy of prematurity areas of capillary non-perfusion can be found angiographically in the areas of oxygen induced obliteration of immature capillaries.[2,3] These areas of the retina have for a long time been considered as sites of liberation of angiogenic substances causing fibrovascular proliferation in retinopathy of prematurity.[1,4,5] In retinopathy of prematurity, however, in contrast to other proliferative retinopathies, there are two kinds of avascular retinal tissue: the primary avascular retina in the periphery where retinal vessels have not yet been formed during ontogenesis, and the secondary avascular retina at the site where the vessels have been destroyed by oxygen (Fig. 1). During intrauterine life the primary avascular retina is in a state of mild hypoxia, which is believed to stimulate the growth of the vessels into it.[6] Following oxygen administration to premature infants mesenchymal tissue ceases to penetrate the originally avascular retina. Thus it may be assumed that this part of the retina becomes more and more anoxic with the lapse of time. It therefore seems possible that angiogenic factors are also produced in the primary avascular retina.

This paper reports a study of the activity of the primary and secondary avascular retina of kittens with oxygen induced retinopathy.

Material and methods

Studies were carried out on eight adult female cats and their 27 newborn kittens. Proliferative retinopathy was induced in the kittens by placing them on the second day of their life in an 80% oxygen environment for 72 h. They were then moved to room

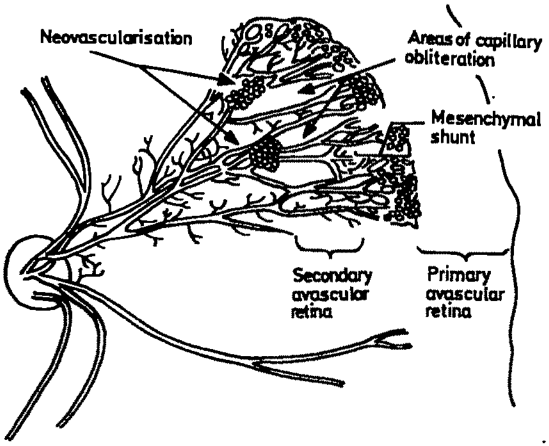

Fig. 1 *Scheme of retinal changes in the initial active stages of retinopathy of prematurity.*

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air until day 21 of life. After this period in eight kittens the retina was excised under the microscope, and $1{\cdot}5\times1{\cdot}5$ mm sections were prepared in the primary and secondary avascular retina according to the technique of Federman *et al.*[7] The sections of each kitten's retina were implanted immediately into the 3×4 mm pockets of their mother's cornea, made according to the technique of Gimbrone *et al.*[8] The distal margin of the pocket was 1 mm from the corneal limbus. The pockets were not made in the axis of rectus muscles, where the sclera is more extensively vascularised.[9] Two pockets were made in each eye. In the right eye retinal sections from the primary avascular retina were implanted into the pockets, whereas in the left eye were implanted those from the secondary avascular retina. For grading the proliferation of vessels in the cornea the author used his own four-grade scale.

In 19 other kittens the retina was also prepared and its sections were implanted into the chicken chorioallantoic membrane of 40 embryos. In 20 of them the sections came from the primary avascular retina and in 20 from the secondary avascular retina. Implantations were performed according to the technique of Lutty *et al.*[10] The rate of inward growth of the membrane vessels was graded by the author's four-grade scale worked out for this purpose.

Because of the small amount of available material retinal extracts could not be made. Therefore, whole sections of the retina were implanted in both procedures.

In the control group, in which proliferative retinopathy was not induced, studies were carried out on eight mother cats and their 21 2-day-old kittens, 80 chicken embryos, and four adult cats. Two-day-old kittens were used because, as observations had shown, the size of their peripheral avascular retina corresponded to that of the primary avascular retina in kittens with proliferative retinopathy. In 21-day-old normal kittens the retina was almost totally vascularised, and hence it was impossible to carry out studies. In eight kittens sections were prepared from the peripheral avascular part of the retina. These were implanted into the pockets in the cornea of the right eye of the kittens' mother, while sections from the peripheral part of the vascularised part of the retina were implanted into pockets in the left eye of their mothers. In the same way retinal sections were prepared in the other 13 kittens and grafted into the chorioallantoic membrane of 40 chicken embryos (20 with peripheral avascular and 20 with peripheral vascularised retina). In four adult cats only pockets were made in the cornea, without tissue grafting. In addition sections of normal kitten's cornea were grafted to the chorioallantoic membrane in 20 chicken embryos and sections of the chorioallantoic membrane in the other 20 chicken embryos. The results were statistically analysed by Student's *t*-test.

Results

Evaluation of neovascular growth of limbal vessels after grafting of the studied tissues into a corneal pocket. After 4–5 days the vessels of the limbus started to invade the cornea at the site of the pocket. After 7–8 days they reached the tissue graft in the pocket. Their maximum growth was visible after about 12 days, and from day 21 their slow disappearance was observed. The extension of vessels in the cornea was graded on day 14 on the basis of a four-grade scale developed on the basis of observations of the cornea with grafted tissues. The individual grades corresponded to the following changes in the cornea.

0: No penetration of vessels into the cornea.

I: Single vessels not more than 5 visible in the cornea in area of the pocket.

II: The number of extending vessels exceeded 5, but they were present only in the area of the pocket (Fig. 2).

III: Further increase in the number of vessels

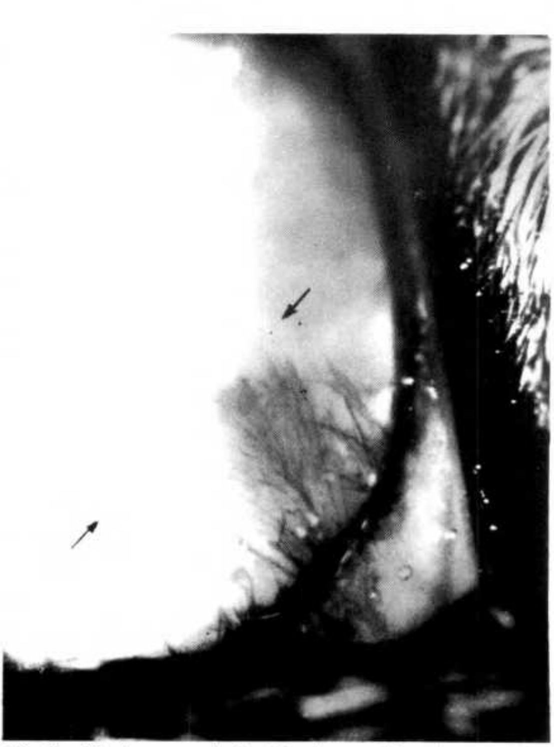

Fig. 2 *II° of neovascularisation after grafting of secondary avascular retina of kittens with oxygen induced retinopathy into a corneal pocket (size of the pocket marked by arrows).*

Table 1 *Neovascular response of limbal vessels after grafting of the studied tissues into a corneal pocket*

No.	*Kind of grafted tissue*	*n*	*Mean*	*SD*	*p*
1	Primary avascular retina in kittens with oxygen induced retinopathy	16	2·93	0·68	a*
2	Secondary avascular retina in kittens with oxygen induced retinopathy	16	2·56	1·03	a
3	Avascular peripheral retina of normal kittens	16	0·87	0·50	b
4	Vascular peripheral retina of normal kittens	16	2·50	0·96	a
5	Corneal pocket without grafted retinal tissue	16	0·00		c

*Means with different letters differ significantly ($p<0·001$) from each other.

which extended also to parts of the cornea adjacent to the pocket.

IV: The width of the front of the invading vessels was twice as large as the width of the pocket in the cornea.

The results in grades (2 from each eye) were summed up in each animal group and the mean was calculated (Table 1).

Evaluation of neovascular response of the chorioallantoic membrane after grafting of the tissues. The extent of blood vessels penetration was determined on the basis of a four-grade scale which was developed from observations of the chorioallantoic membrane with grafted tissues. The individual grades of the scale corresponded to the following changes of blood vessels of the chorioallantoic membrane.

0: No changes in the configuration of blood vessels.

I: Concentric penetration of small vessels of the membrane into the grafted tissue was seen, but the changes observed did not cover in all more than two quadrants.

II: Penetrating blood vessels were found in all quadrants of the membrane surrounding the grafted tissue. Changes were also observed in the course of medium vessels.

III: Further medium blood vessels of the membrane started to penetrate the graft (Fig. 3).

IV: Concentric penetration of big vessels into the grafted tissue could be seen, which often formed extended loops in the centre.

The results obtained in the grades were summed up in each group of animals and the mean was calculated (Table 2).

Discussion

The corneal micropocket technique and chorioallantoic assay are widely used by many investigators in studies of angiogenic activity of various tissues.[1 7-10 12-14] These two assay systems have therefore been used to study this activity in the primary and secondary avascular retina of kittens. The studies showed that, in oxygen treated kittens with proliferative retinopathy, angiogenic activity of the primary

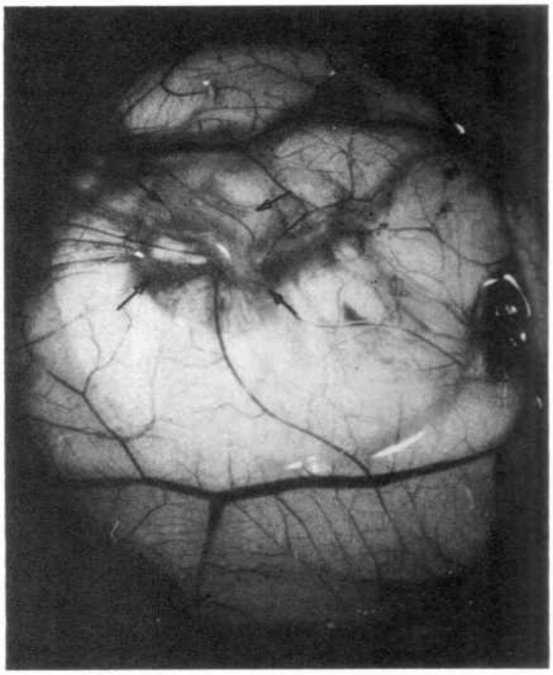

Fig. 3 *III° of neovascularisation after grafting of primary avascular retina of kittens with oxygen induced retinopathy on chicken chorioallantoic membrane (site of graft indicated by arrows).*

Table 2 *Neovascular response of chorioallantoic membrane after grafting of the studied tissue*

No.	*Kind of grafted tissue*	*n**	*Mean*	*SD*	*p*†
1	Primary avascular retina in kittens with oxygen induced retinopathy	14	2·42	0·85	a
2	Secondary avascular retina in kittens with oxygen induced retinopathy	14	2·53	0·90	a
3	Avascular peripheral retina of normal kittens	15	0·93	0·79	b
4	Vascular peripheral retina of normal kittens	13	2·30	0·75	a
5	Chorioallantoic membrane of chicken embryo	18	0·00		c
6	Normal cornea of kittens with oxygen induced retinopathy	17	0·00		c

*The number of results in the particular groups is smaller than 20 because some embryos died during studies.

†Means with different letters differ significantly ($p<0·001$) from each other.

avascular retina increased considerably (about three times) in comparison with the activity of its anatomically corresponding peripheral avascular retina of control animals. This activity in the primary avascular retina was equal to that of the secondary avascular retina. A similar activity was also observed in the peripheral part of the vascularised part of the retina of control kittens; this area anatomically corresponds to the secondary avascular retina. These results indicate that the major effect of oxygen treatment is a considerable increase in the angiogenic activity of the primary avascular retina.

The reason for the change in angiogenic activity seems to be the gradually increasing hypoxia of the primary avascular retina. During the development of normal retinal vessels in intrauterine life the penetration of blood vessels to the peripheral avascular retina is stimulated by its relative hypoxia occurring during maturation.[6] However, no considerable hypoxia of the retina arises, because gradually developing blood vessels provide an oxygen supply.

The situation changes if oxygen is administered in excess to a premature infant or an experimental animal. Obliteration of immature blood vessels of the retina causes mesenchymal tissue to cease to proliferate and it accumulates in the form of a mesenchymal shunt (Fig. 1). Although differentiation and maturation of the retina itself are progressing, they are not accompanied by the development of its blood vessels.[15] In such a condition the retinal tissue becomes more and more hypoxic. Oxygen deficiency leads to disturbances in tissue metabolism and liberation of angiogenic substances. In most cases regression of the ability of the mesenchymal tissue to proliferate is observed, and blood vessels again penetrate into avascular retina, liquidating its hypoxia (known as spontaneous regression). If, however, regression does not occur, hypoxia of the primary avascular retina becomes more critical, which in consequence increases liberation of angiogenic factors in this tissue, as is reported in this paper.

The theory of progressing hypoxia of the primary avascular retina was also confirmed by the experimental studies of Ernst and Goldstick.[16] These authors found that, in kittens with proliferative retinopathy after oxygen treatment, preretinal oxygen pressures above the avascular retina were close to 0 mmHg. This was found to be caused by increased oxygen utilisation by the avascular retina after oxygen treatment, and not by a decreased flow in the choroidal vessels.[16] Thus it may be assumed that in retinopathy of prematurity maturation of the avascular retina itself is progressing despite the inhibition of vascularisation, which leads to its hypoxia.

The data obtained in this paper indicate that the angiogenic activity was similar in both the primary avascular and secondary avascular retina. It seems, however, that a more important role in the pathogenesis of retinal neovascularisation in retinopathy of prematurity is played by the primary avascular retina. As is known, the severity of proliferative retinopathies depends on the size of the area of retinal ischaemia.[1] In retinopathy of prematurity the incidence and severity of the disease are directly proportional to the prematurity degree[1 7-19]—that is, to the size of the primary avascular retina.

Fibrovascular proliferation in the vitreous may assume very different proportions in retinopathy of prematurity. Changes of similar intensity are also found in diabetic retinopathy. Angiographic studies in this disease show that the occurrence of changes is preceded by the appearance of large areas of capillary non-perfusion.[1] In retinopathy of prematurity the primary avascular retina is an area of comparable size. The secondary avascular retina covers a small area of the ocular fundus,[2] and angiogenic factors released in this area could not be the reason for such great changes.

Recent studies of Taylor *et al.*[14] showed that extracts of whole retinas from kittens with oxygen induced retinopathy contained about 3 times more angiogenic factors than did extracts of normal retinas from control animals. These studies indicate that in the retina of kittens with proliferative retinopathy after oxygen treatment there exist large areas with considerably raised angiogenic activity, as compared with retinas of healthy animals. These areas cannot be identified with the secondary avascular retina, because the area covered by it is small, and it would not change the angiogenic activity of the total retina. The area of the primary avascular retina is sufficiently large to cause these changes.

Retinopathy of prematurity as a rule does occur once the retina is completely vascularised[20-22]—that is, after the disappearance of the primary avascular retina. Cogan's studies, however, have shown that maturation of retinal blood vessels may last for a longer time after the ora serrata is reached.[23] Thus, if the occurrence of changes depended on the secondary avascular retina, retinopathy of prematurity could also occur after complete vascularisation of the retina, because immature vessels are still present then.

If it is admitted that in the pathogenesis of retinopathy of prematurity the primary avascular retina has a decisive role, it becomes clear why cicatricial tissue primarily develops in the periphery of the fundus. The ischaemic theory assumes that proliferation of blood vessels and the cicatricial tissue accompanying them develop in the direction of the site in which the concentration of angiogenic factors is highest.[11] In retinopathy of prematurity cicatricial tissue develops first of all above the primary avascular retina. If the angiogenic factors were produced mainly in the secondary avascular retina, cicatricial changes would develop further posteriorly the higher the degree of prematurity, which is not in agreement with clinical observations.

The results of this paper and the above considerations may support the following conception of pathogenesis of retinopathy of prematurity. Destruction of immature retinal blood vessels by oxygen results in inhibition of the development of vasoformative mesenchymal tissue and in stopping normal vascularisation of the peripheral parts of the retina. This causes a gradual increase of hypoxia of the primary avascular retina and increases liberation of angiogenic factors which are responsible for proliferation of blood vessels. Hypoxia and liberation of these factors also occur in the area of the secondary avascular retina. However, this is not of main importance in the pathogenesis of retinopathy of prematurity because of the very small area of this part of the retina.

However, it should be emphasised that the above mentioned conception of pathogenesis of retinopathy of prematurity has not yet been completely proved. It was based on the results of experimental studies in which a corneal micropocket technique and chorioallantoic assay were used. Both tests are liable to wide variations, if only because no two animals are ever exactly alike. One cannot be sure either that the volume of tissue implanted is precisely the same in all the test conditions and that the distance between the corneal implant and the limbus is exactly equal throughout. However, despite these limitations it seems that this conception may be found acceptable.

The results of this paper may also have a practical value. It is widely believed that in proliferative retinopathies destruction of ischaemic areas of the retina were angiogenic factors are liberated may bring the vascular proliferation under control and so arrest the disease.[1] The present results indicate that destruction of the primary avascular retina—for example, by cryotherapy—should be the most effective method in the treatment of retinopathy of prematurity.

References

1 Patz A. Clinical and experimental studies on retinal neovascularization. *Am J Ophthalmol* 1982; **94:** 715–43.

2 Flynn JT, O'Grady GE, Herrera JA, Kushner BJ, Cantolino S, Milam W. Retrolental fibroplasia: I. Clinical observations. *Arch Ophthalmol* 1977; **95:** 217–23.

3 Payne JW, Patz A. Fluorescein angiography in retrolental fibroplasia. In: Patz A, Fine SL, eds. Interpretation of fundus fluorescein angiogram. *Int Ophthalmol Clin* 1977; **17:** 121–35.

4 Ashton N. The pathogenesis of retrolental fibroplasia. *Ophthalmology* 1979; **86:** 1695–9.

5 Ashton N, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. *Br J Ophthalmol* 1954; **38:** 397–432.

6 Ashton N. Oxygen and the growth and development of retinal vessels. *Am J Ophthalmol* 1966; **62:** 412–35.

7 Federman JL, Brown GC, Feldberg NT, Felton SM. Experimental ocular angiogenesis. *Am J Ophthalmol* 1980; **89:** 231–7.

8 Gimbrone MA Jr, Leapman SB, Cotran RS, Folkman J. Tumor growth and neovascularization: an experimental model using the rabbit cornea. *J Natl Cancer Inst* 1974; **52:** 413–27.

9 Chen C-H, Chen SC. Angiogenic activity of vitreous and retinal extracts. *Invest Ophthalmol Vis Sci* 1980; **19:** 596–602.

10 Lutty GA, Thompson DC, Gallup JY, Mello RJ, Patz A, Fenselau A. Vitreous: an inhibitor of retinal extract-induced neovascularization. *Invest Ophthalmol Vis Sci* 1983; **23:** 52–6.

11 Ben Ezra D. Neovasculogenesis. Triggering factors and possible mechanism. *Surv Ophthalmol* 1979; **24:** 167–76.

12 Glaser BM, D'Amore PA, Michels RG, *et al.* The demonstration of angiogenic activity from ocular tissues. *Ophthalmology* 1980; **87:** 440–6.

13 Kissun RD, Hill CR, Garner A, Phillips P, Kumar S, Weiss JB. A low-molecular-weight angiogenic factor in cat retina. *Br J Ophthalmol* 1982; **66:** 165–9.

14 Taylor CM, Weiss JB, Kissun RD, Garner A. Effect of oxygen tension on quantities of procollagenase-activating angiogenic factor present in the developing kitten retina. *Br J Ophthalmol* 1986; **70:** 162–5.

15 Nissenkorn I, Kremer I, Ben-Sira I, Cohen S, Garner A. A clinicopathological case of retinopathy of prematurity (ROP) treated by peripheral cryopexy. *Br J Ophthalmol* 1984; **68:** 36–41.

16 Ernst JT, Goldstick TK. Retinal oxygen tension and oxygen reactivity in retinopathy of prematurity in kittens. *Invest Ophthalmol Vis Sci* 1984; **25:** 1129–34.

17 Kalina RE, Karr DJ. Retrolental fibroplasia. Experience over two decades in one institution. *Ophthalmology* 1982; **89:** 91–5.

18 Kinsey VE, Arnold JH, Kalina RE, *et al.* PaO_2 levels and retrolental fibroplasia: a report of the cooperative study. *Pediatrics* 1977; **60:** 655–68.

19 Majima A. Studies on retinopathy of prematurity. I. Statistical analysis of factors related to occurrence and regression in active phase. *Jpn J Ophthalmol* 1977; **21:** 404–20.

20 Patz A. The role of oxygen in retrolental fibroplasia. *Graefes Arch Klin Exp Ophthalmol* 1975; **195:** 77–85.

21 Patz A. Studies on retinal neovascularization. *Invest Ophthalmol Vis Sci* 1980; **19:** 1133–8.

22 Patz A, Payne JW. Retrolental fibroplasia. In: Duane TD, ed. *Clinical ophthalmology*. Hagerstown: Harper and Row, 1985 update: 3: chapter 20.

23 Cogan D. Development and senescence of the human retinal vasculature. *Trans Ophthalmol Soc UK* 1963; **83:** 465–89.

Accepted for publication 20 March 1987.

British Journal of Ophthalmology, 1988, **72**, 368–369

A modified irrigating-aspirating needle

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SUMMARY To facilitate the safe and thorough evacuation of cortical lens debris in extracapsular extractions the author has modified the coaxial irrigating-aspirating cannula. The modified needle has a 45° bend 10 mm from its tip. The tip is rendered slightly bulbous, thus eliminating the step between the outer sleeve and the coaxial portion. This prevents snagging of the posterior capsule and eliminates sleeve slide. The needle has been found especially helpful in deeply recessed eyes, and, when it was rotated, cortical cleaning from the equatorial and superior portions of the capsular bag was easier than with a straight needle. There were no posterior capsular breakages in 54 consecutive cases of the use of this needle.

The safe and thorough evacuation of cortical lens matter continues to remain one of the extracapsular surgeon's main problems and priorities. While working within the confines of the capsular bag has simplified this task, difficulties continue to present themselves. A particular problem, often exaggerated by the use of the Honan's bulb, is a tendency, especially noted in older, thinner patients, for the eye to become markedly enophthalmic. This, coupled with a prominent supraorbital ridge, renders the introduction of the coaxial needle at the correct plane into the capsular bag exceedingly difficult. Indeed, the steepness of the approach may be such that rupture of the posterior capsule, particularly when cortical material is being cleaned from the inferior portion of the bag, becomes a real possibility.

To address this particular difficulty the author has modified the original coaxial needle. The modified needle (Fig. 1) adheres to the same basic principle as the standard one, but 10 mm from the tip, there is a

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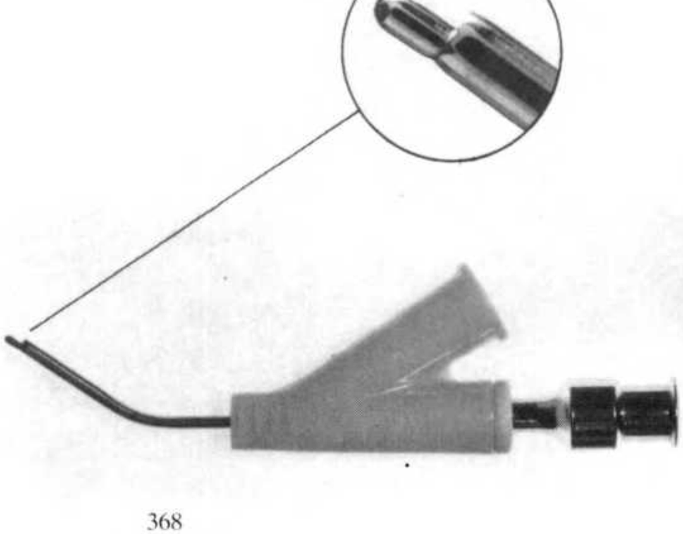

Fig. 1 *The modified needle.*

45° bend. This not only greatly facilitates the introduction of the coaxial needle into the capsular bag, but enables the active portion of the needle to be more easily kept parallel to the posterior capsule when in the bag, despite a deeply recessed eye.

By rotating the needle the port itself can be positioned, so that equatorial cleaning of the capsular bag is more readily achieved. Manipulations in the 12 o'clock position are also considerably easier with this curved needle.

The length of the projecting tip of the needle has been standardised at 1·5 mm, and it has been rendered slightly bulbous inferiorly and at the sides to eliminate the step between the inner and the outer sleeve at these points, thus reducing the possibility of snagging the posterior capsule and effectively eliminating sleeve slide. The port itself remains a 0·3 mm circular opening, and is placed superiorly 0·5 mm from the tip. As the outer sleeve is now fixed, it is thought that all variables associated with the coaxial needle have been eliminated. Finally, the irrigating tubing connects at a 45° angle posteriorly, and there is controlled movement of this outer casing on the coaxial needle. This prevents the drip tube encroaching on the field of vision and reduces the possibility of the drip feed line snagging on the head towels during manipulation within the eye.

Using the needle over a two-month period the author has carried out 54 consecutive extracapsular lens extractions, of which 52 were implanted with a posterior chamber lens, the two non-implanted cases being preoperatively designated so. The Honan's bulb and sodium hyaluronate (Healonid) were used in all cases. Of the 54 patients 32 had general anaesthesia. Their ages ranged between 47 and 91 years. There were no posterior capsular breakages.

The Docherty modified irrigating-aspirating needle is manufactured by Steriseal Ltd, of Redditch.

The author expresses grateful thanks to Mr Barry Wilks in the Department of Medical Illustration at the Derbyshire Royal Infirmary, and Mr P R Cund, Hypodermic Production Manager at Steriseal Ltd.

Accepted for publication 12 March 1987.

British Journal of Ophthalmology, 1988, **72**, 370–376

K-Sol corneal preservation at room temperature

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SUMMARY K-Sol, a recently developed corneal storage medium that contains purified chondroitin sulphate in tissue culture medium (TC 199), is capable of preserving corneal tissue for 14 days at 4°C. To study the effect of tissue storage in K-Sol at room temperature we preserved rabbit corneas in K-Sol and M-K medium for three or seven days at 25°C. All of the corneal endothelial sheets were intact after three days. At seven days the change in pH of the K-Sol medium was less than that of M-K medium. Corneas preserved in M-K medium showed swelling of mitochondria and a decrease in the number of cytoplasmic organelles. Corneas preserved in K-Sol had organised cytoplasmic organelles and nuclei. Scanning electron micrographs revealed well preserved endothelial sheets. Corneas stored in the two media showed no significant difference in thickness. A pair of human corneas preserved in K-Sol at room temperature for six days maintained about 95% of the endothelial sheet in good condition. Small separations were observed between some of the endothelial cells. However, even in these areas, the cytoplasmic organelles were well preserved. It appeared that K-Sol is more stable than M-K medium at room temperature, and that both rabbit and human corneas can be preserved in good condition in K-Sol for at least six days at 25°C.

Kaufman and others developed a new corneal preservation medium (K-Sol) for storing corneal tissue for at least two weeks at refrigerator temperature.[1-3] K-Sol contains 2·5% purified chondroitin sulphate in tissue culture medium (TC-199), 0·025 M HEPES buffer, and gentamicin sulphate. The pH is 7·4 and the osmolality is 310 mosm. Refrigerator preservation is simple and inexpensive; however, temperature control is uncertain during shipping. At temperatures higher than 4°C the metabolic activity of the cornea increases, and the survival of the endothelial cells is threatened by the release of metabolic wastes into the medium.[4] We examined the stability of K-Sol, as well as the ability of this medium to preserve rabbit and human corneas, at room temperature.

Material and methods

Animal care and treatment in this investigation were in compliance with the ARVO resolution on the use of animals in research. Twelve New Zealand albino rabbits were killed with an overdose of sodium pentobarbital. The eyes were immediately enucleated and the globes flooded with gentamicin sulphate.

The corneas were sectioned from the eyeball with a 2 to 3 mm scleral rim and placed epithelial side down. All procedures were carried out by sterile technique in a laminar flow hood. The right corneas were preserved in K-Sol and the mate corneas were preserved in M-K medium, both at room temperature (25°C) for three or seven days (six pairs each). The media were not changed during this study. When the corneas were removed from the medium, the pH of the medium was measured. The corneas were fixed in 2·5% glutaraldehyde and 3% formalin with 0·1 N sodium cacodylate trihydrate buffer (pH 7·35) for 12

Table 1 *Rabbit corneal thickness after preservation at 25°C*

Preservation time	*Corneal thickness* (mm) (mean±SD)*		*Statistically significant difference*
	K-Sol	*M-K medium*	
3 days	0·33±0·03 (n=8)	0·34±0·02 (n=4)	No
7 days	0·41±0·02 (n=4)	0·42±0·06 (n=4)	No

*Control thickness=0·34 mm.

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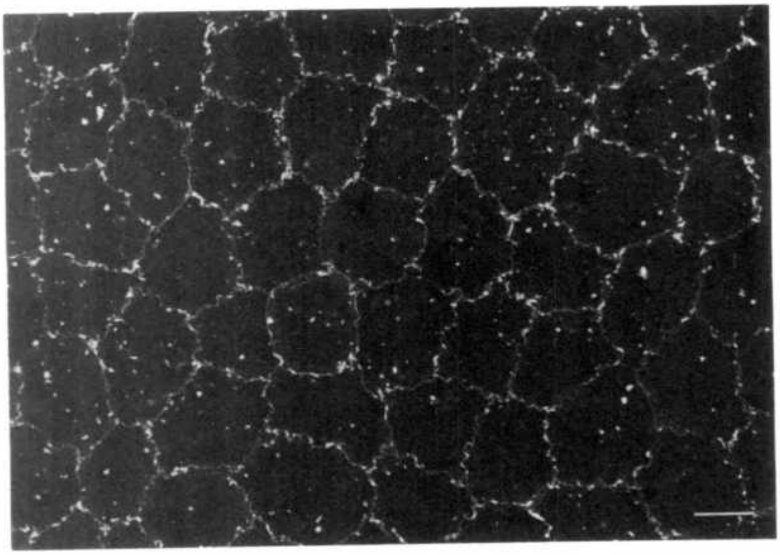


Fig. 1A *Scanning electron micrograph of rabbit corneal endothelial cells preserved in K-Sol for three days at room temperature. Normal mosaic-like endothelial cells are seen. The endothelial surface is smooth and the overlapping interdigitations can be seen clearly. Bar=10 µm.*

hours, washed in the same buffer, postfixed in buffered 1% osmium tetroxide for 90 minutes, washed again in buffer, and dehydrated in graded alcohols from 50% to 100% and propylene oxide.

Half of each cornea was embedded in Epon. Embedded specimens were sectioned with a microtome and stained with toluidine blue for light microscopy or uranyl acetate and lead citrate for transmission electron microscopy. Corneal thickness was measured on light micrographs which were enlarged 100 times.

For scanning electron microscopy the other half of each cornea was fixed in 2·5% glutaraldehyde and 3% formalin with 0·1 N sodium cacodylate trihydrate buffer (pH 7·35) for 12 hours, dehydrated in alcohol, dried in a critical point dryer, placed on aluminium stubs, coated with gold, and photographed.

A pair of corneas from a 33-year-old human donor was obtained 2 hours and 25 minutes post mortem, placed in K-Sol by the eye bank, and stored at room temperature for six days. The corneas were prepared for scanning electron microscopy and transmission electron microscopy, and corneal thickness was measured as described above.

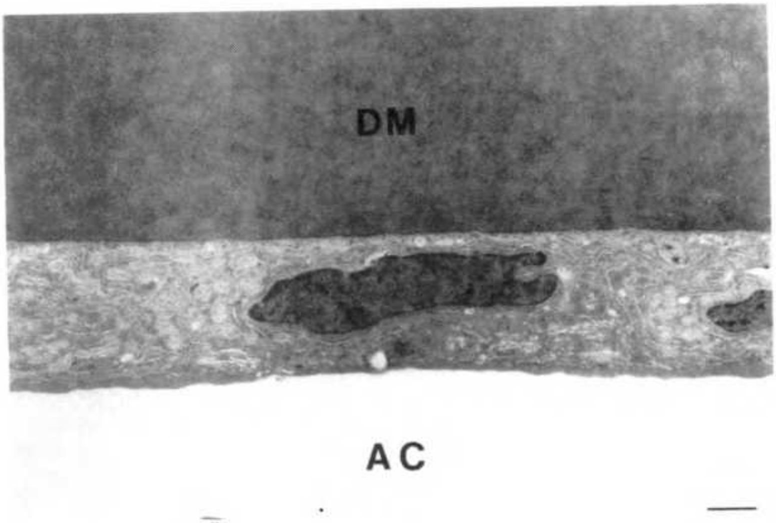


Fig. 1B *Transmission electron micrograph of the same cornea. The nucleus and cytoplasmic organelles are preserved intact. Bar=1 µm.*

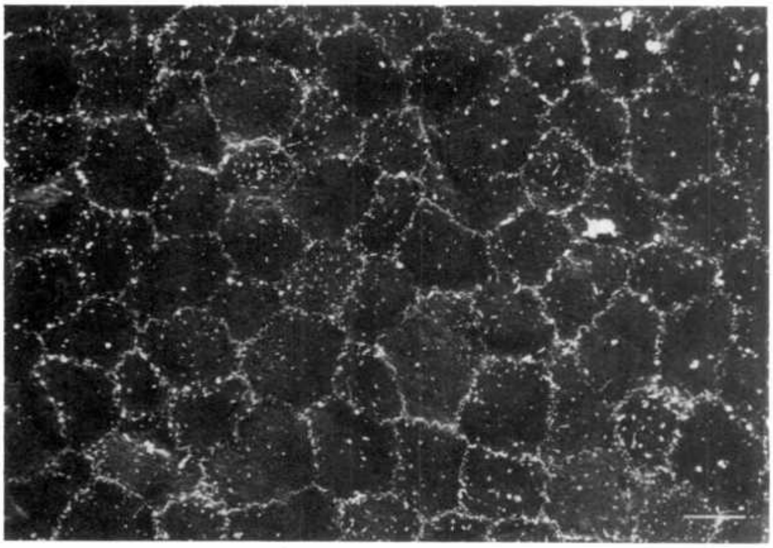


Fig. 2A *Scanning electron micrograph of rabbit corneal endothelial cells preserved in K-Sol for seven days. The mosaic-like pattern of the endothelial sheets can be seen. The lateral cytoplasmic borders are comparatively distinct. Cellular pleomorphism is visible and the endothelial surface is ruffled. Bar=10 µm.*

Results

pH AND CORNEAL THICKNESS

The pH was measured in two samples of each medium at three and seven days. Both K-Sol and M-K medium had a pH of 7·40 before use. The average pH was 7·28 for the K-Sol and 7·15 for M-K medium at three days. After seven days the average pH was 7·17 for K-Sol and 7·04 for M-K medium. The average pH of the K-Sol in which the human corneas were stored was 7·27 after six days.

At three days the average thickness of the corneas stored in K-Sol was 0·33 mm (SD 0·03) and of the corneas stored in M-K medium 0·34 mm (SD 0·02). After seven days, corneal thickness was 0·41 mm (SD 0·04) in the K-Sol preserved corneas and 0·42 mm (SD 0·06) in the M-K medium preserved corneas. The difference was not statistically significant (Table 1).

HISTOLOGY

The appearance of the endothelial cells was similar in all specimens. The rabbit corneas preserved in K-Sol for three days at room temperature showed normal mosaic-like endothelial sheets with normal overlapping interdigitations of the cells (Fig. 1A). The cytoplasmic organelles (mitochondria, Golgi apparatus, and rough endoplasmic reticulum) were

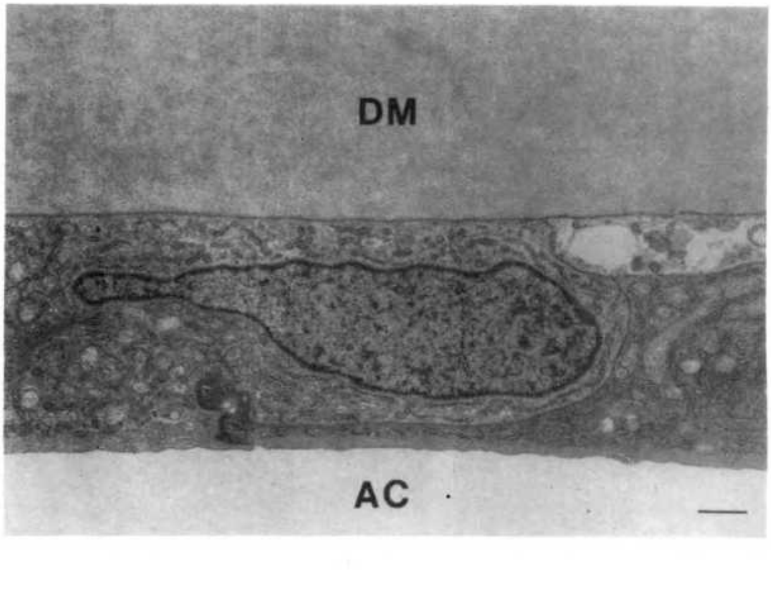


Fig. 2B *Transmission electron micrograph of the same cornea. The thickness of the endothelial cells is increased (4·7 µm). The cytoplasm is less dense anterior to the nucleus. The cytoplasmic organelles and nucleus are preserved in good condition. Bar=1 µm.*

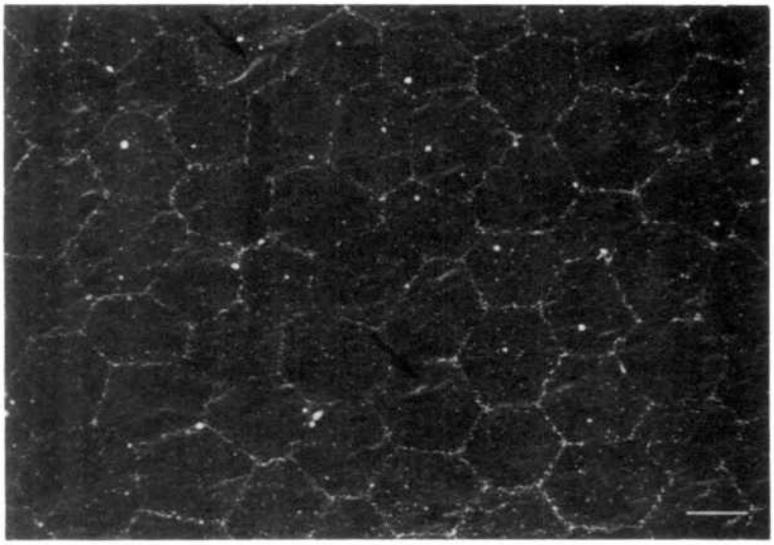


Fig. 3A *Scanning electron micrograph of rabbit corneal endothelial cells preserved in M-K medium for three days at room temperature. Normal mosaic-like endothelial sheets are seen. Some of the endothelial surface is ruffled (arrows). Bar=10 μm.*

intact, and the nucleus was dense (Fig. 1B). With seven-day preservation the mosaic-like pattern of the endothelial sheets could be seen, and the lateral cell borders were relatively distinct. Cellular pleomorphism and ruffling of the endothelial surface were visible (Fig. 2A). Compared with the corneas stored for three days, which were 3·2 μm thick, the corneas stored for seven days showed an increase in corneal thickness to 4·7 μm, and the cytoplasmic density was somewhat decreased anterior to the nucleus. However, the endothelial cells were organised and appeared to be in good condition (Fig. 2B).

The rabbit corneas preserved in M-K medium for three days at room temperature showed normal mosaic-like endothelial sheets. Some of the endothelial surfaces were slightly ruffled (Fig. 3A). Transmission electron microscopy revealed intact endothelial cells. The density of the cytoplasmic organelles was slightly decreased anterior to the nucleus (Fig. 3B). After seven days of preservation, mosaic-like hexagonal endothelial sheets, as well as cellular pleomorphism and ruffling of the surface membrane, were seen (Fig. 4A). Transmission electron microscopy revealed a decrease in the numbers of cytoplasmic organelles, and the mitochondria were swollen. These changes were more prominent anterior to the nucleus (Fig. 4B).

The human corneas preserved in K-Sol for six days

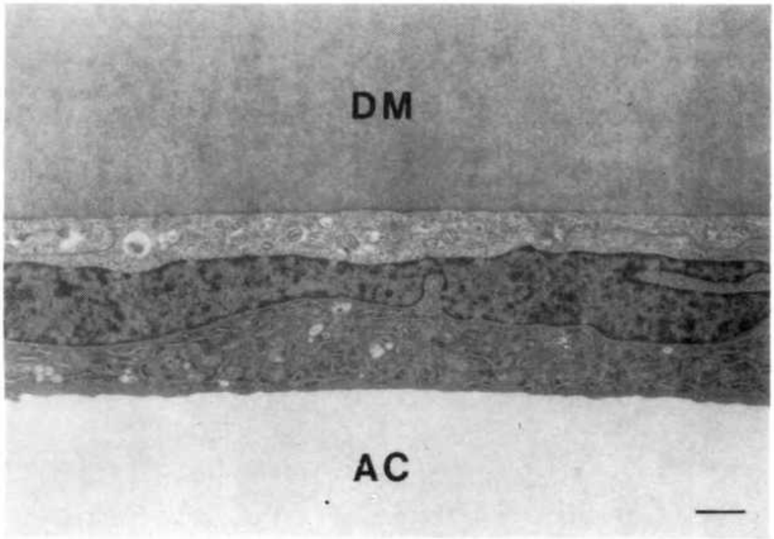


Fig. 3B *Transmission electron micrograph of the same cornea. Cytoplasmic organelles anterior to the nucleus are fewer in number and small vacuolations can be seen. The endothelial cells are almost intact. Bar=1 μm.*

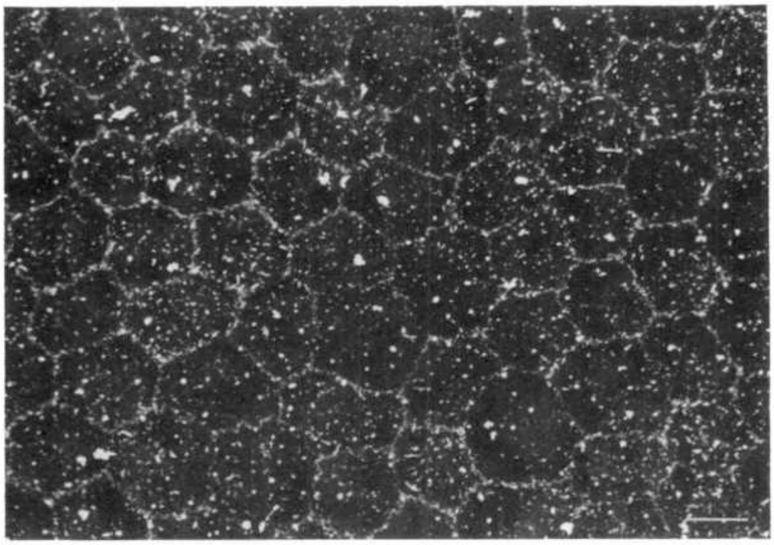


Fig. 4A *Scanning electron micrograph of rabbit corneal endothelial cells preserved in M-K medium for seven days at room temperature. Mosaic-like hexagonal endothelial sheets, cellular pleomorphism, and ruffling of the endothelial surface can be seen. Bar=10 µm.*

at room temperature showed no stromal swelling by light microscopy. The average central corneal thickness was 0·49 mm. The mosaic-like pattern of endothelial sheets was visible, but the lateral cytoplasmic membranes were somewhat indistinct, and there were some endothelial surface protrusions in about 5% of the endothelial cells along the lateral cytoplasmic membranes (Fig. 5A). The endothelial cells were 2–3 µm thick and appeared attenuated, but were generally preserved in good condition (Fig. 5B). Small intercellular separations could be seen between some of the endothelial cells. Most of the endothelial cells showed well preserved, organised cytoplasmic organelles (Fig. 5C) and nuclei.

Discussion

Rabbit corneal endothelial cells were ultrastructurally intact after storage for three days at room temperature in both K-Sol and M-K medium. At seven days corneas preserved in K-Sol were still in good condition. The cytoplasmic organelles and nuclei were well preserved. However, corneas preserved in M-K medium showed mitochondrial swelling and fewer cytoplasmic organelles. These histological observations suggest that K-Sol preserves rabbit corneas better than M-K medium at room temperature. In addition the pH of K-Sol was more stable than that of M-K medium, although both

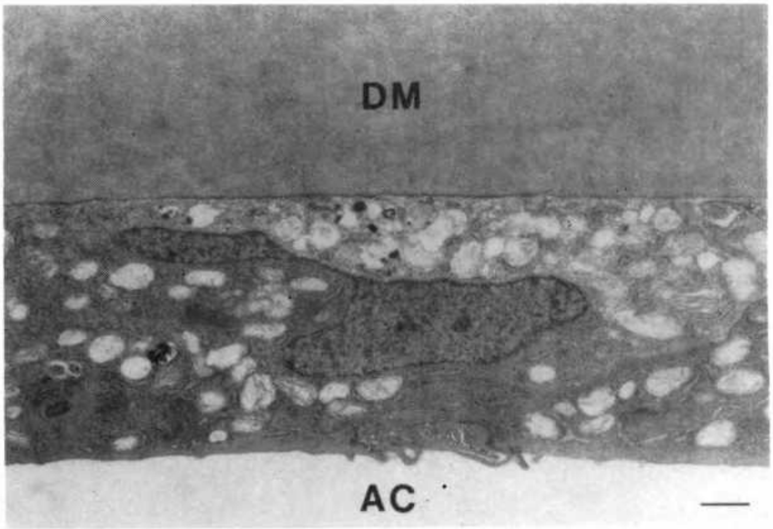


Fig. 4B *Transmission electron micrograph of the same cornea. The endothelial cells are thicker (5·1 µm) than the cells on corneas stored in M-K medium for three days (3·5 µm). Fewer cytoplasmic organelles are seen, and mitochondrial swelling is prominent anterior to the nucleus. Bar=1 µm.*

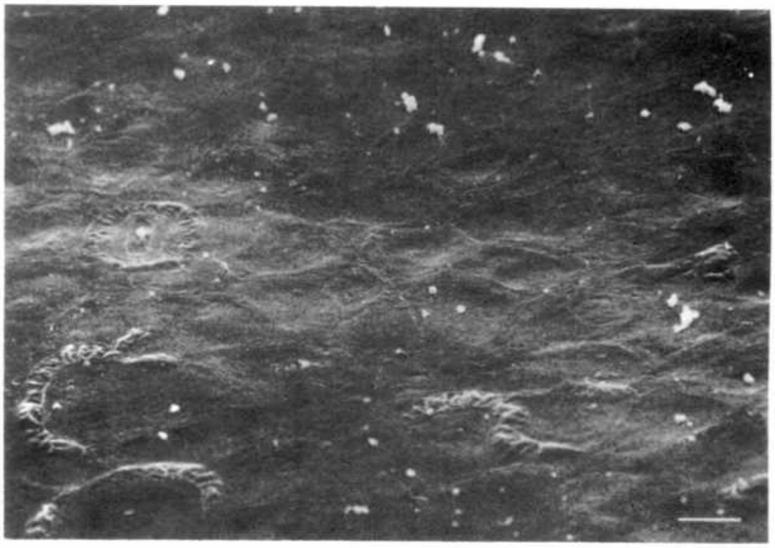


Fig. 5A *Scanning electron micrograph of the human corneal endothelial cells preserved in K-Sol for six days at room temperature. The mosaic-like pattern of the endothelial sheets can be seen. The lateral cytoplasmic membranes are indistinct. Some of the cytoplasmic membranes protrude along the lateral cytoplasmic membranes. Bar=10 µm.*

media maintained pH in the optimum range (6·8 to 8·2)[5] for maintenance of corneal endothelial integrity and function.

Sachs and his colleagues[4] reported disorganised cytoplasmic organelles in human corneas preserved for four days in M-K medium at room temperature. In our study human corneal endothelial cells preserved in K-Sol medium at room temperature were still in good condition after six days. The cytoplasmic organelles and nuclei were intact. Scanning electron microscopy revealed a few protrusions on the surface of about 5% of the endothelial cells (Fig. 5A), which corresponded to small intercellular separations seen by transmission electron microscopy (Fig. 5C). However, the cytoplasmic organelles were still well preserved even in the protruding areas. It appears that K-Sol preserves human corneas better than M-K medium at room temperature for six days.

There was no significant difference in corneal thickness between K-Sol and M-K medium preserved rabbit corneas. No stromal swelling was seen in these or in the human corneas preserved in K-Sol. Recently Lindstrom and others[6] reported that chondroitin sulphate prevents stromal swelling and preserves corneal endothelial cells in organ culture. K-Sol, which contains purified chondroitin sulphate, demonstrates this ability also in room temperature preservation.

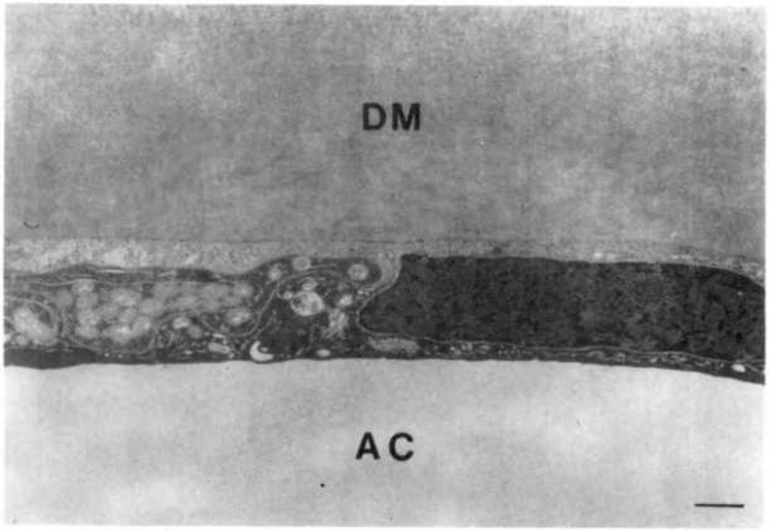


Fig. 5B *Transmission electron micrograph of the same cornea. Endothelial cells are attenuated (2–3 µm). Almost all endothelial cells show intact cytoplasmic organelles and nuclei. Bar=1 µm.*

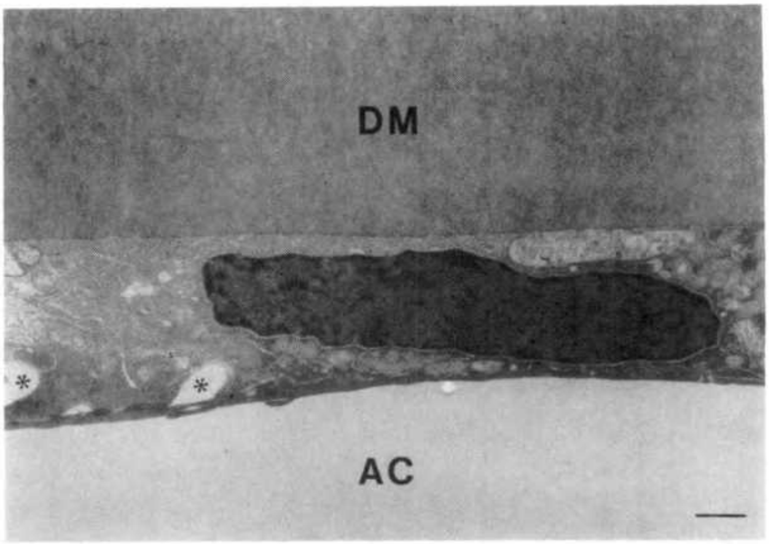


Fig. 5C *Transmission electron micrograph of the human corneal endothelial cells. Small intercellular separations (*) can be seen between some of the endothelial cells, but the cytoplasmic organelles in these cells are still well preserved. Bar=1 µm.*

Previously Lindstrom and his colleagues[7] suggested that room temperature preservation eliminates the need for an incubator or refrigerator, reducing the expense and complexity of temperature maintenance. However, room temperature preservation requires a completely sterile technique to prevent infection. For this reason refrigerator preservation seems safer and easier than room temperature preservation.

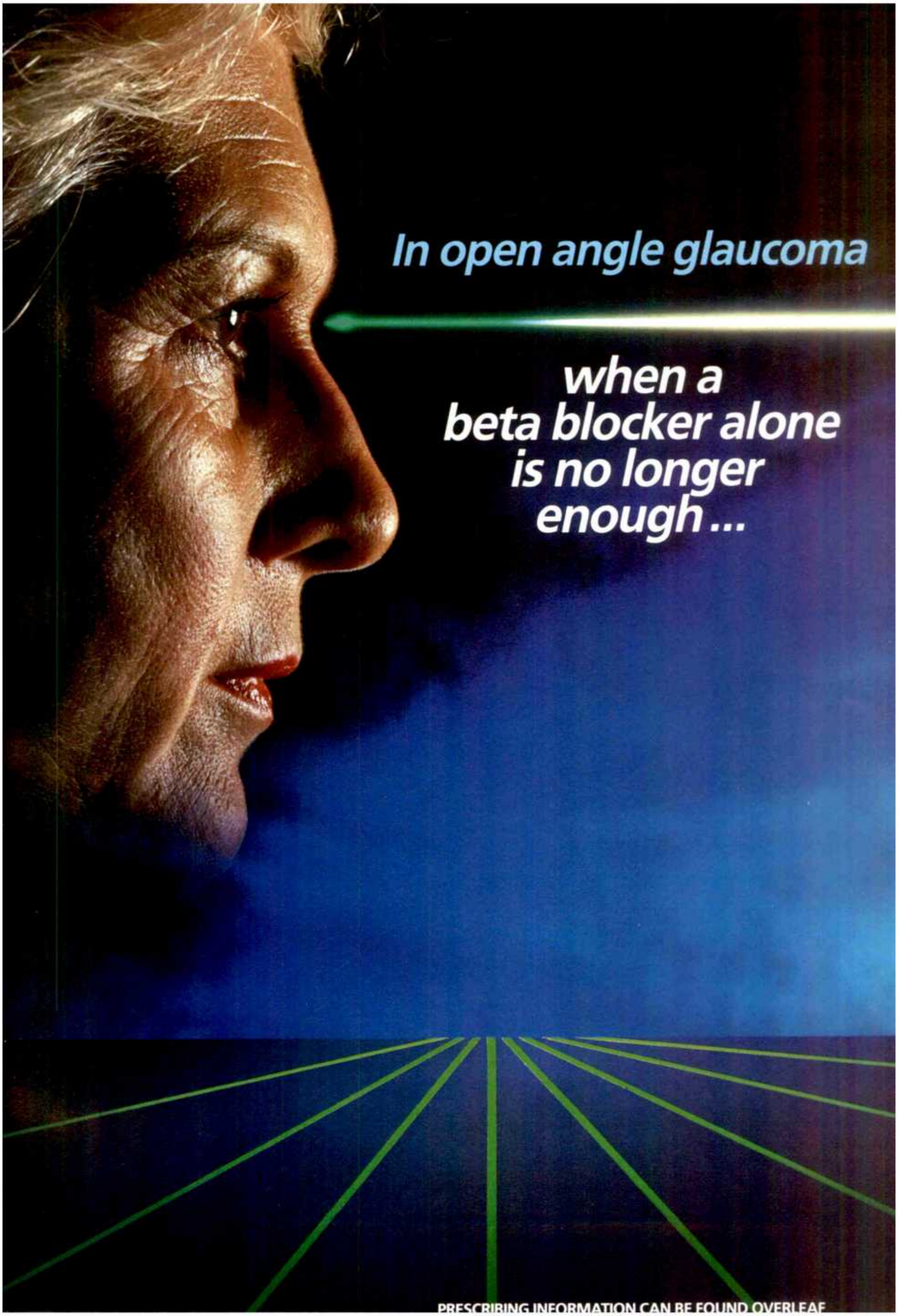
We are not suggesting that room temperature preservation be considered as an alternative to the widespread practice of refrigerator storage of donor corneal tissue, but we have shown here that tissue stored in K-Sol can successfully withstand some period of time at room temperature and remain intact. The ability to preserve corneas at room temperature would make the shipping of donor tissue for long distances and to areas without reliable refrigeration easier and safer, thereby increasing the utilisation of available tissue and reducing wastage.

This study was supported in part by Public Health Service grants EY02580 and EY02377 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland.

References

1 Kaufman HE, Varnell ED, Kaufman S. Chondroitin sulfate in a new corneal preservation medium. *Am J Ophthalmol* 1984; **98:** 112–4.
2 Kaufman HE, Varnell ED, Kaufman S, Beuerman RW, Barron BA. K-Sol corneal preservation. *Am J Ophthalmol* 1985; **100:** 299–304.
3 Yau CW, Kaufman HE. A medium-term corneal preserving medium (K-Sol). *Arch Ophthalmol* 1986; **104:** 598–601.
4 Sachs V, Goldman K, Valenti J, Kaufman HE. Corneal storage at room temperature. *Arch Ophthalmol* 1978; **96:** 1075–7.
5 Edelhauser HF, Gonnering R, Van Horn DL. Intraocular irrigating solutions. *Arch Ophthalmol* 1978; **96:** 516–20.
6 Lindstrom RL, Skelnik DL, Mindrup EA, Doughman DJ. Organ culture corneal preservation with chondroitin sulfate. ARVO abstract. *Invest Ophthalmol Vis Sci* 1984; **25** (suppl): 266.
7 Lindstrom RL, Doughman DJ, Van Horn DL, Schmitt MK, Byrnes PJ. Organ culture corneal storage at ambient room temperature. *Arch Ophthalmol* 1977; **95:** 869–78.

Accepted for publication 12 March 1987.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British Journal of Ophthalmology, 1988, 72, 377–379

Ophthalmic complications with disseminated intravascular coagulation

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SUMMARY Massive lid oedema, ecchymosis, proptosis with a total restriction of extraocular movement, markedly raised intraocular pressure, and occlusion of the central retinal artery developed acutely in the right eye of a 26-year-old woman with a past history of disseminated intravascular coagulation. She had been admitted to hospital for symptoms of abdominal pain and bleeding from multiple sites a few hours earlier. Five days previously she had some proptosis of the other eye and had been treated with antibiotics for suspected orbital cellulitis at another hospital. The oedema and proptosis resolved on high-dose intravenous corticosteroid therapy. Despite attempts to relieve the orbital oedema and raised intraocular pressure with a lateral canthotomy and antiglaucoma medications, the patient lost all perception of light in the right eye and has subsequently developed an optic nerve atrophy.

Disseminated intravascular coagulation (DIC) is a syndrome involving widespread intravascular coagulation, primarily in small vessels. Associated disorders have included head trauma, sepsis, surgery, burns, obstetrical complications, liver disease, malignancy, and inflammatory bowel disease.[1 2] Common to these is the incitement of the coagulation cascade, with resultant thrombosis. Consumption of clotting elements eventually leads to hypocoagulability and haemorrhage.[1] Reported ocular complications include thrombosis of choroidal and retinal vessels, as well as bleeding in the optic nerve sheath, vitreous, choroid, and retina.[3-5] Similar problems are seen in the brain, heart, kidney, gastrointestinal and genitourinary tracts, as well as involvement of other organs.[1 5]

Case report

A 26-year-old woman presented to the University Hospital with severe abdominal pain, headache, and bleeding from the urinary tract, rectum, vagina and nose. She had ecchymosis of the knees and buttocks and petechiae of the hard palate. Generalised oedema, most marked in the head and neck regions, and massive lid oedema with proptosis were present.

Five days prior to this admission the patient had noted fever, proptosis, and lid oedema of her left eye and was admitted to another hospital. Although there was no evidence of sinusitis or a history of penetrating injury, she was treated with oral and intravenous antibiotics for orbital cellulitis. Orbital symptoms and signs progressed slowly despite treatment. On the day of transfer to the University Hospital the unaffected right eye became acutely proptotic.

She had a history of colitis and DIC. The first episode of DIC occurred two and one-half years previously during an active period of colitis when the patient was five months pregnant. Generalised oedema, including facial swelling, was present at that time. The patient improved on prednisone and sulphasalazine therapy. Six months before the present admission she had been in hospital again with DIC. She improved with the addition of prednisone to the maintenance sulphasalazine therapy. Ophthalmic complications were not present during either episode.

Our examination revealed a blind right eye, and uncorrected near vision of 20/200 in the left eye. Pronounced lid oedema, proptosis, and haemorrhagic conjunctival chemosis were present (Fig. 1). Intraocular pressure by Schiøtz tonometry was

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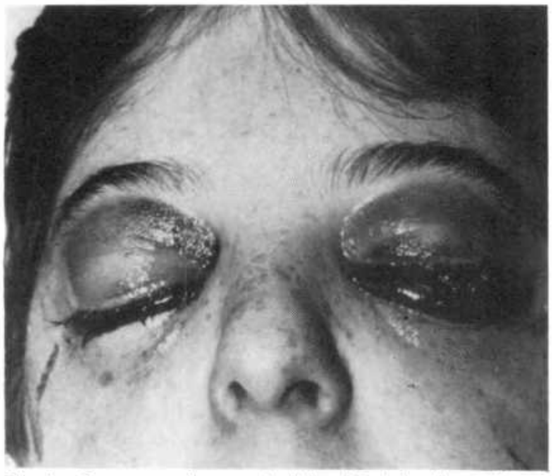

Fig. 1 *Pronounced proptosis, lid and facial ecchymosis, and oedema, conjunctival chemosis, and haemorrhage are evident on each side.*

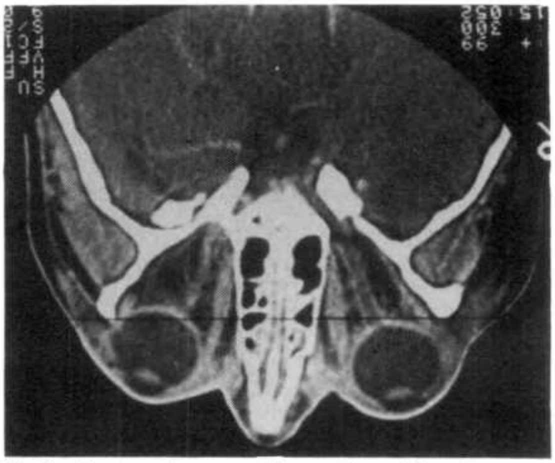

Fig. 2 *Computed tomographic scan shows bilateral proptosis, greater on the right side, thickening of extraocular muscles, and increased radiodensity of optic nerve suggestive of haemorrhages within the sheaths.*

greater than 80 mmHg in the right eye and 11 mmHg in the left eye. There was no extraocular motility of the right eye; there was approximately 50% of normal abduction and adduction of the left eye. Ophthalmoscopic examination revealed narrowed retinal arterioles and diffuse retinal oedema with a cherry red macula in the right eye; the fundus of the left eye appeared normal. There was no evidence of intraocular inflammation in either eye.

Laboratory data from the referring hospital included a platelet count of 160×10^9/l, a prothrombin time (PT) of 25 seconds, a partial thromboplastin time (PTT) of 100 seconds, a fibrinogen level of 0·29 g/l, and a fibrin split product (FSP) titre of 1:2560. Repeat laboratory studies at the time of admission showed the platelet count had decreased to 69×10^9/l; the erythrocyte sedimentation rate was 7 mm/h (Westergren). Serological studies for antinuclear antibody titre, rheumatoid factor, and complement levels gave normal results. A pregnancy test was negative. Blood and conjunctival cultures were negative. Computerised tomographic examination of the orbits showed bilateral proptosis, thickening of the muscle outlines, and increased radiodensity of the optic nerves (Fig. 2).

Initial treatment included intravenous administration of 125 mg methylprednisolone followed by intravenous dexamethasone 25 mg every 6 hours for four doses and then 20 mg every 6 hours for four doses. A right lateral canthotomy with division of the canthal tendon was performed. No significant blood was drained by this manoeuvre, though the tenseness of the orbital tissues was noticeably relieved. In the subsequent seven hours the intraocular pressure in the right eye fell to 29 mmHg. Vision has remained no light perception in the right eye but improved to 20/40 in the left eye over 12 hours and to 20/20 over several days. Orbital oedema and proptosis gradually resolved, but the right eye slowly developed optic atrophy.

Discussion

Among the multiple extraintestinal manifestations of inflammatory bowel disease is hypercoagulability resulting from abnormal coagulation factors and platelets.[6] This may have precipitated the episodes of DIC in our patient. Talbot *et al.*[2] observed DIC in three patients with inflammatory bowel disease, one of whom also had sepsis. Endo *et al.*[7] described DIC in two patients with ulcerative colitis; however, in both patients the DIC followed a surgical procedure.

This patient's coagulopathy probably involved the ophthalmic, maxillary, and episcleral vessels, resulting in ischaemia, haemorrhage, and massive oedema. These factors may have led to an increased episcleral venous pressure, to raised intraocular pressure, and eventually to central retinal artery occlusion. In carotid-cavernous fistula the arterialisation of all orbital vessels may lead to an increased intraocular pressure.[8] Presumably this occurs secondary to a raised episcleral venous pressure. Alternatively, optic nerve ischaemia or thrombus formation in the central retinal artery may have contributed to visual loss.

The extraocular muscle dysfunction presumably resulted from massive oedema, though ischaemia to the muscles themselves is a possibility. No restriction was present on forced duction testing. Periorbital oedema has been described in a patient with thrombotic thrombocytopenic purpura.[9] We can only speculate as to whether the mechanisms may have been the same.

Many arterial and venous complications have been reported as sequelae of inflammatory bowel disease with or without DIC, including central retinal arterial occlusion.[2 10–12] Proptosis and lid oedema have been reported in a patient with orbital pseudotumour and Crohn's disease; we believe our patient's course to be too rapid and the oedema too massive to be explained on such a basis.[13] Since our patient did not show any ocular signs of inflammation, we do not believe the inflammation associated with Crohn's disease (that is, uveitis or optic neuritis) was a likely contributing cause of visual loss.[10 14]

Other possible explanations of our patient's course might include vasculitis or infection,[15] but there were no clinical or laboratory data to support a diagnosis of either. Fever is known to occur in patients with colitis.

The ophthalmic complications we report here are rare in DIC. To our knowledge the sudden development of massive orbital oedema, markedly raised IOP, and occlusion of the central retinal artery has not been reported previously. Since the administration of high doses of intravenous corticosteroids decreased the oedema rather quickly, it is reasonable to assume that this therapy, along with adequate decompression undertaken shortly after the initial development of the orbital oedema, might have averted the subsequent series of ocular complications.

References

1 Hamilton PJ, Stalker AL, Douglas AS. Disseminated intravascular coagulation: a review. *J Clin Pathol* 1978; **31**: 609–19.

2 Talbot RW, Heppell J, Dozois RR, Beart RW Jr. Vascular complications of inflammatory bowel disease. *Mayo Clin Proc* 1986; **61**: 140–5.

3 Ortiz JM, Yanoff M, Cameron JD, Schaffer D. Disseminated intravascular coagulation in infancy and in the neonate. *Arch Ophthalmol* 1982; **100**: 1413–5.

4 Azar P, Smith RS, Greenberg MH. Ocular findings in disseminated intravascular coagulation. *Am J Ophthalmol* 1974; **78**: 493–6.

5 Cogan DG. Ocular involvement in disseminated intravascular coagulopathy. *Arch Ophthalmol* 1975; **93**: 1–8.

6 Lam A, Borda IT, Inwood MJ, Thomson S. Coagulation studies in ulcerative colitis and Crohn's disease. *Gastroenterology* 1975; **68**: 245–51.

7 Endo K, Miura N, Sato T, *et al.* Two cases of ulcerative colitis complicating disseminated intravascular coagulation. *Jpn J Gastroenterol* 1982; **79**: 1778–82.

8 Sanders MD, Hoyt WF. Hypoxic ocular sequelae of carotid-cavernous fistulae. *Br J Ophthalmol* 1969; **53**: 82–97.

9 Percival SPB. The eye and Moschcowitz's disease. A review of 182 cases. *Trans Ophthalmol Soc UK* 1970; **90**: 375–82.

10 Heuer DK, Gager WE, Reeser FH. Ischemic optic neuropathy associated with Crohn's disease. *J Clin Neuro-Ophthalmol* 1982; **2**: 175–81.

11 Schneiderman JH, Sharpe JA, Sutton DMC. Cerebral and retinal vascular complications of inflammatory bowel disease. *Ann Neurol* 1978; **5**: 331–7.

12 Kehoe EL, Newcomer KL. Thromboembolic phenomena in ulcerative colitis. *Arch Intern Med* 1964; **113**: 711–5.

13 Young RSK, Hodes BL, Cruse RP, Koch KL, Garovoy MR. Orbital pseudotumor and Crohn's disease. *J Pediatr* 1981; **99**: 250–2.

14 Hopkins DJ, Horan E, Burton IL, Clamp SE, De Dombal FT, Goligher JC. Ocular disorders in a series of 332 patients with Crohn's disease. *Br J Ophthalmol* 1974; **58**: 732–7.

15 Owyang C, Miller LJ, Lie JT, Fleming CR. Takayasu's arteritis in Crohn's disease. *Gastroenterology* 1979; **76**: 825–8.

Accepted for publication 20 March 1987.

British Journal of Ophthalmology, 1988, 72, 380–385

Sudden visual loss associated with clostridial bacteraemia

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SUMMARY A patient with endogenously acquired *Clostridium septicum* panophthalmitis is presented. The patient exhibited a striking sequence of signs and symptoms associated with this devastating ocular infection. Intensive antibiotic therapy was ineffective and enucleation of the globe was required. The microscopic pathology of the enucleated globe showed extensive infarction and necrosis of ocular structures in association with the panophthalmitis. In addition thrombosis of the central retinal artery and of choroidal vessels was observed.

Clostridial ocular infections usually result from penetrating injuries of the globe, and the offending species is typically *Clostridium perfringens*.[1] There have been only two previously reported cases where acute endophthalmitis has occurred secondarily to clostridial sepsis.[2,3] This paper describes a case of clostridial panophthalmitis occurring subsequent to an endogenous clostridial infection, and discusses possible mechanisms of the ocular pathology observed. It is presented to make ophthalmologists aware of the occurrence of clinical and pathological findings associated with a clostridial ocular infection following systemic clostridial sepsis.

Case report

A 77-year-old white male physician was admitted to Penobscot Bay Medical Center on 1 February 1986 with a 24-hour history of fever, chills, and right upper quadrant pain. He reported acute, bloody diarrhoea 10 days prior to admission which resolved without antibiotic treatment. Stool examination at that time revealed 1+ white blood cells, but cultures were negative for enteric pathogens. He had a history of emphysema and chronic atrial fibrillation, adenocarcinoma of the prostate gland, thought to have been cured by transurethral resection in 1985, and chronic constipation, but was otherwise in good health. He had continued to practise medicine until this present illness.

Physical examination revealed a Caucasian male appearing acutely ill with abdominal pain, mild diaphoresis, and chills. Vital signs on admission were blood pressure 150/68 mmHg, pulse 100/minute and regular, respiratory rate 32/minute, and temperature 38·9°C. Eye examination by his internist at this time showed the pupils to be equal and reactive to light, and a funduscopic examination showed nothing abnormal. On cardiovascular examination a grade 3/6 systolic murmur was heard. The abdominal examination revealed decreased bowel sounds, with diffuse tenderness, especially in the right upper quadrant. There was no rebound or guarding tenderness. On rectal examination no masses were felt. Occult blood was detected in the stools. The remainder of the physical examination was unremarkable.

Laboratory data on admission showed a white cell count of $23{\cdot}7\times10^9/l$, with 88 polymorphonuclear cells and 10 band forms per 100 cells. The haemoglobin was 13·1 g/dl and the packed cell volume (haematocrit) was 0·37. Other significant values include a blood urea nitrogen level of 24 mg/dl (4·0 mmol/l), creatinine of 1·3 mg/dl (115 μmol/l), and a decreased total protein and albumin of 5·2 g/dl (52 g/l) and 2·9 g/dl (29 g/l), respectively. Radiological examination included chest, anteroposterior plane film of the abdomen, biliary tree scan, and intravenous pyelogram. All these studies were within normal limits. A peritoneal lavage was negative for red blood cells. The differential diagnosis at this time included subacute bacterial endocarditis, pneumonia, or a primary abdominal process such as

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cholecystitis, perforation of a viscus from diverticulitis, or malignancy. Blood cultures were obtained, and intravenous clindamycin and gentamicin were begun.

Six hours after admission to hospital the patient complained of left periorbital pain and reported sudden and complete visual loss in his left eye. An ophthalmic consultation was promptly obtained. Ocular examination at this time revealed no light perception with the left eye. The right eye was entirely normal. External eye examination was significant for marked left eyelid and orbital swelling. The conjunctiva of the left eye was injected with 2+ chemosis and a mucopurulent drainage was present. The cornea had stromal and epithelial oedema. The iris colour was blue-grey bilaterally. The left pupil was larger than the right (2·5 mm compared with 1·5 mm) and did not respond to either direct or consensual stimulation. Details of the fundus could not be seen in the left eye by either direct or indirect ophthalmoscopy. Extraocular movements were severely restricted in all directions. The tension by Schiøtz tonometry was 60 mmHg in the left eye.

Left orbital aspiration was attempted but no fluid was obtained. The patient received topical pilocarpine, Propine (dipirefrim HCl 0·1%), and timolol, as well as intravenous acetazolamide. Ocular examination three hours later revealed a tension of 30 mmHg in the left eye, and the iris colour had now changed from blue-grey to reddish brown. Slit-lamp examination, which was initially deferred owing to the patient's poor condition, was performed eight hours after the onset of blindness. It showed a left anterior chamber that contained large sections of both pigmented material and white, flocculent material (0·25 mm in diameter) suspended in a gel which occupied approximately 90% of the anterior chamber. A diagnosis of panophthalmitis and orbital cellulitis was made, and the patient was put on topical gentamicin in addition to systemic antibiotics.

On the third day in hospital the patient developed a corneal ulcer. Blood cultures obtained on admission grew *Clostridium septicum*, and antibiotic therapy was changed to intravenous oxacillin and chloramphenicol, and subconjunctival gentamicin was administered. On the fifth day in hospital a corneal perforation was noted and the eye was enucleated next day (Fig. 1). A significant finding at enucleation was the ischaemic appearance of the extraocular muscles. Later that evening the patient developed bilateral pleural effusions. His clinical condition gradually improved, yet he died on the thirteenth hospital day of an apparent cardiac arrest.

The cause of death at necropsy was determined to be a rupture of a dissecting lower thoracic aortic aneurysm with exsanguination into the left pleural space. The rupture occurred 5 cm above the diaphragm, and was surrounded by a 1–2 cm area of mottled, organising thrombus. There was also an area of dissection in the abdominal aorta near the origin of the inferior mesenteric artery. Microscopic sections of both of these aortic regions showed extensive atheromatous plaque formation, with acute and chronic inflammation adjacent to areas of dissection. Within these areas were foci of degenerating polymorphonuclear leucocytes, suggesting recent bacterial infection. Examination of the heart revealed calcification and moderate narrowing of the coronary vasculature. Internal examination showed normal myocardium and valve structure except for a 5–6 mm area of pink speckling on the posterior aortic valve leaflet. Microscopic examination of this speckled area revealed extravasation of erythrocytes in the intimal and subintimal connective tissue. Cross-sections of the entire length of the ophthalmic arteries from the internal carotids to the globe on the right, and to the point of enucleation of the left globe showed no thrombus formation or inflammation. The lumen of the left internal carotid was reduced by one-half by a calcified, atherosclerotic plaque (Fig. 2). There was no evidence of meningitis, cerebral ischaemia, or thrombosis of cerebral vessels. Examination of the visceral structures was remarkable only for numerous diverticula in the sigmoid colon.

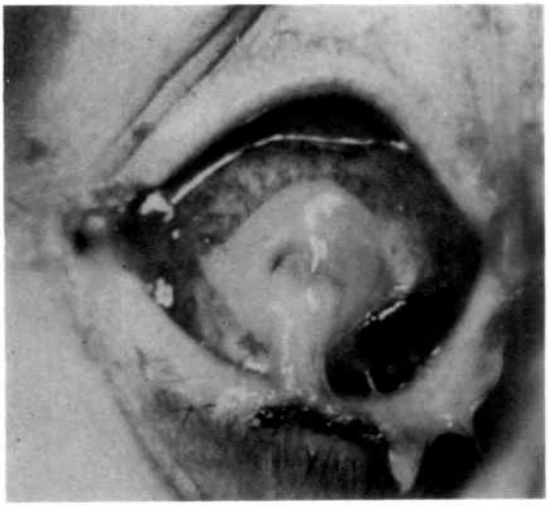

Fig. 1 *Clinical photograph of left eye with central corneal perforation just prior to enucleation.*

The left globe measured 21 mm vertically by 20 mm horizontally by 24 mm axially and had 5 mm of attached optic nerve. The cornea measured 11 mm by 10 mm and was opaque with a central perforation 4 mm in diameter. The pupil was not visible and the

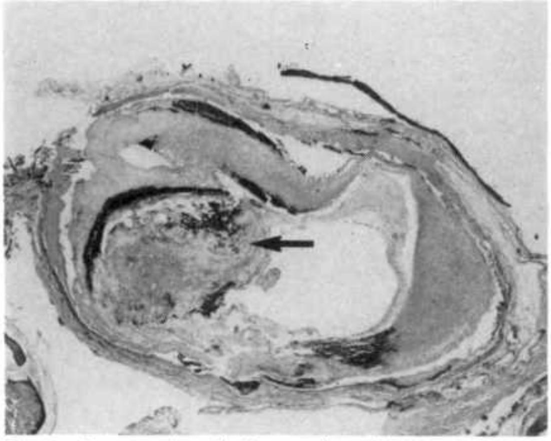

Fig. 2 *Cross-section of left internal carotid artery with diameter reduced to one-half by calcified, atheromatous plaque (arrow). Haematoxylin and eosin, ×5.*

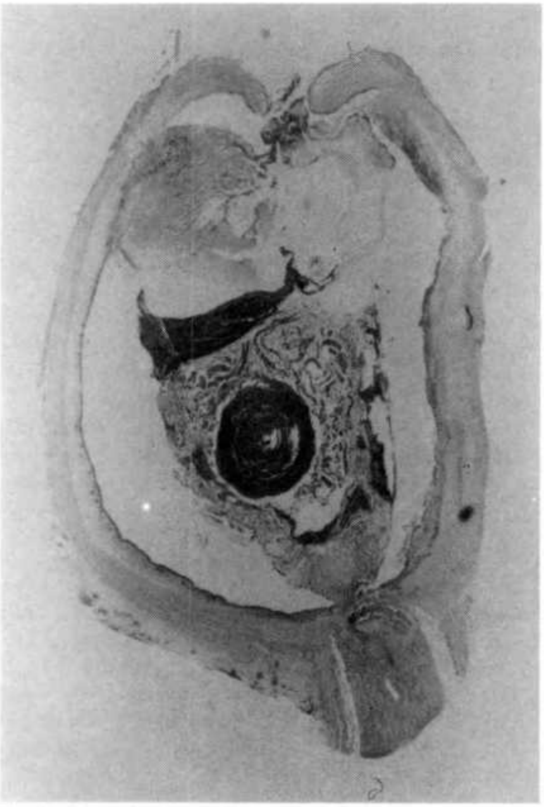

Fig. 3 *Sagittal section of left eye showing severe panophthalmitis. Full-thickness perforation of central cornea, and thick inflammatory membrane behind the cornea; extensive anterior synechiae are present. The iris and ciliary body are necrotic, as is the retina, which is completely detached. Haematoxylin and eosin, ×3.*

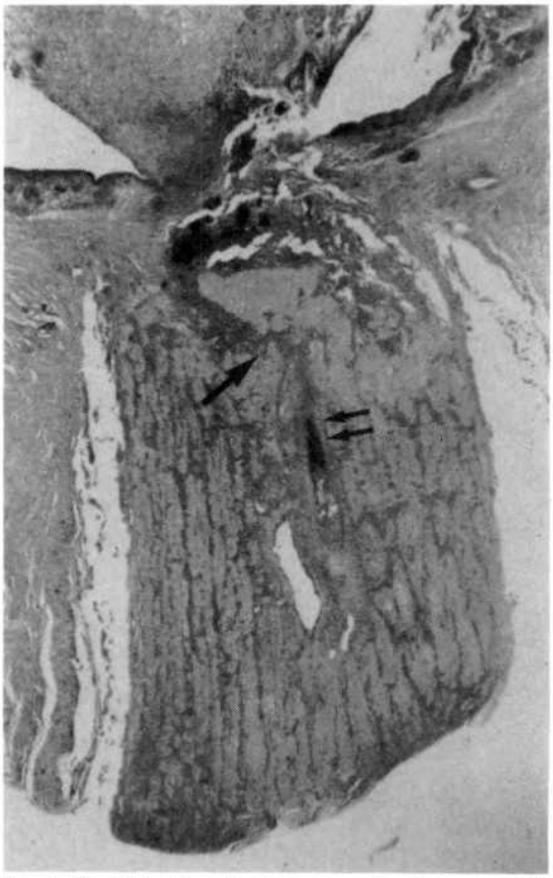

Fig. 4 *Sagittal section of left optic nerve showing an area of central necrosis surrounded by acute inflammation (arrow). An occlusion of the central retinal artery by an organising thrombus is also present (arrows). Haematoxylin and eosin, ×1·7.*

eye did not transilluminate light. On horizontal section the anterior chamber was obliterated and the angle was not visible. The iris, ciliary body, and lens were surrounded by white, flocculent material. The lens was dislocated posteriorly. A haemorrhagic mass filled the vitreous cavity. The retina was totally detached, and the optic disc not visible.

Microscopically there was a large, full-thickness perforation of the central cornea. The eye showed severe panophthalmitis (Fig. 3). The cornea, where present, was covered by a thin layer of epithelium with identifiable Bowmans's membrane. The corneal stroma was infiltrated with polymorphonuclear leucocytes. The residual Descemet's membrane was devoid of endothelium. An inflammatory membrane was present behind the cornea and extensive anterior synechiae were seen. The nasal portion of the iris and ciliary body were necrotic, though the inflammatory

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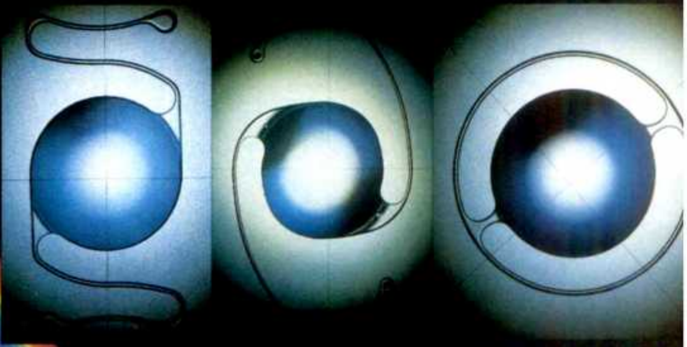

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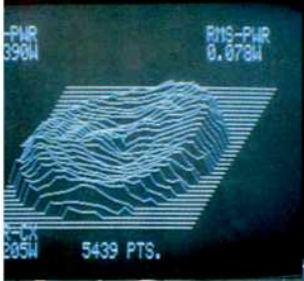

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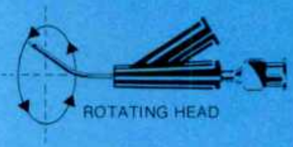

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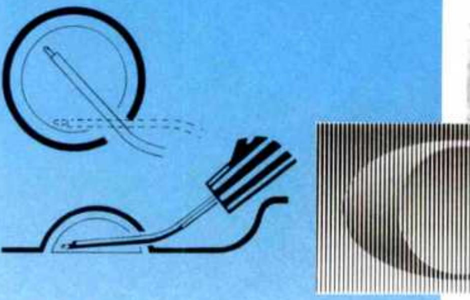

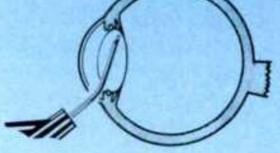

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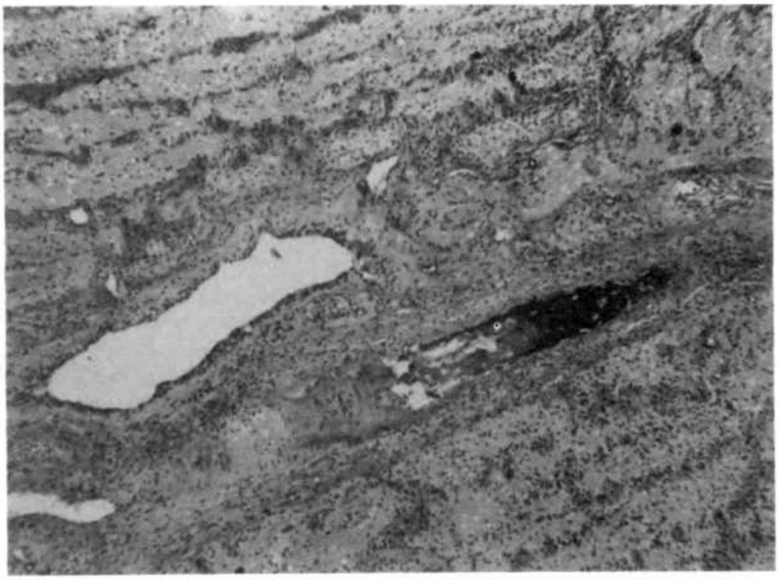

Fig. 5 *Higher magnification of sagittal section through the left optic nerve. The central retinal artery and vein are shown, and the occlusion of the central retinal artery is present. Also evident is the acute inflammatory response involving the left optic nerve. Haematoxylin and eosin, ×16.*

response was most severe in the anterior temporal portion of the eye. The retina was completely detached and necrotic (Fig. 3). Within the optic nerve head was an area of central necrosis surrounded by acute inflammation (Fig. 4). An occlusion of the central retinal artery by an organising thrombus (Figs. 4, 5), and numerous thrombi within the choroidal vasculature were seen. Brown and Brenn stain for Gram-positive and Gram-negative bacteria (Fig. 6) and periodic acid-Schiff stain revealed numerous, large Gram-positive rods in areas of the iris, ciliary body, retina, and optic nerve. Kinyoun's acid fast stain was negative for acid-fast bacilli.

The following diagnoses were made: (1) panophthalmitis secondary to *Clostridium septicum*; (2) corneal perforation; (3) thrombi of the central retinal artery and choroidal vessels.

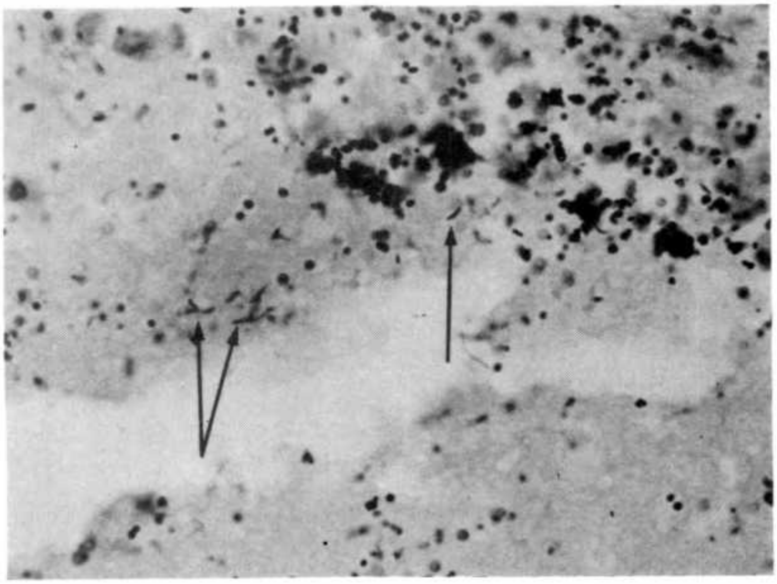

Fig. 6 *High magnification of necrotic retina with several large, spindle-shaped, Gram-positive bacilli present (arrows). Brown and Brenn stain, ×100.*

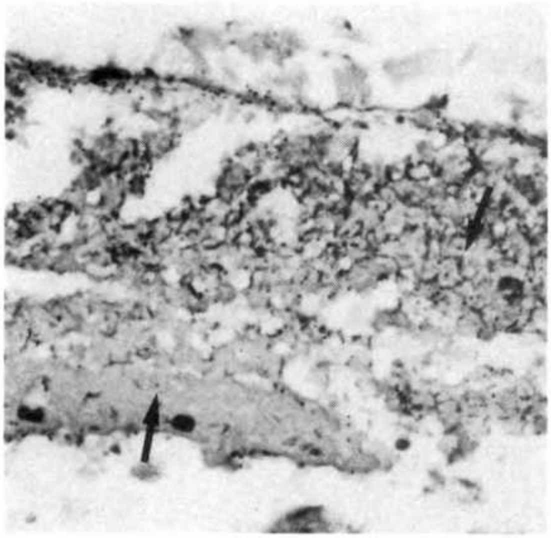

Fig. 7 *Periodic acid-Schiff stain of necrotic retina showing an abundance of positively staining, spindle-shaped rod forms (arrows). ×10.*

Discussion

Gas gangrene panophthalmitis, characterised by Leavelle,[1] typically occurs after penetrating injuries to the globe with subsequent infection of the damaged tissue of *Clostridium perfingens*. This paper describes a patient who developed a panophthalmitis secondary to clostridial septicaemia. The diagnosis of clostridial panophthalmitis was based on the clinical evolution, the gross and histological appearance, and the presence of *Clostridium septicum* detected by anaerobic blood cultures prior to antibiotic treatment. An intraocular culture obtained after antibiotic treatment showed no growth of *Clostridium septicum*, but Gram stains and periodic acid-Schiff stains showed an abundance of Gram-positive, spindle-shaped rods in necrotic areas of iris, ciliary body, retina, and optic nerve. These morphological findings, together with positive blood cultures for *Clostridium septicum*, indicate that this organism was responsible for the fulminant ocular destruction observed in this patient.

A search of the literature reveals only two cases similar to that now described. One patient was a 68-year-old man who had a perforated gangrenous gall bladder and *Clostridium perfringens* sepsis.[2] The second was a 78-year-old woman with acute gastroenteritis and *Clostridium septicum* sepsis.[3] The patient reported here had many of the typical symptoms of clostridial endophthalmitis.[1] He experienced sudden left orbital pain and visual loss accompanied by oedema of the lids and periorbital tissue. In addition a raised intraocular pressure, conjunctival chemosis with a change of iris colour to reddish brown, and eventual corneal ulceration and perforation were observed. No gas bubble in the anterior chamber was present, a finding which has often been described in clostridial panophthalmitis.[1-3]

This patient's clinical history illustrates the possible source of clostridial sepsis and mechanisms responsible for the evolution of the panophthalmitis. Although no certain source of *Clostridium septicum* was discovered during necropsy, it is reasonable to speculate that it came from the gastrointestinal tract. The patient suffered an episode of acute, bloody diarrhoea 10 days before admission to hospital and had no recent history of antibiotic use or ulcerative colitis.

The finding of generalised atherosclerosis at necropsy and the unusual involvement of the abdominal aorta in the region of the inferior mesenteric artery suggest that colonic ischaemia may have been the cause of the bloody diarrhoea. Although the possibility of embolism in a bowel vessel exists in the setting of chronic atrial fibrillation, bowel ischaemia is usually produced by a non-occlusive event.[4] In fact, approximately one-third of patients with mesenteric ischaemia do not have an identifiable occlusion of a major vessel.[4] Although rectal examination was positive for occult blood in the stools, colonoscopy performed when the patient was in hospital did not show any ulcerations, friability, or bulging folds from submucosal haemorrhage. The finding of multiple sigmoidal diverticula on necropsy raises the possibility that a temporary communication between mucosal vasculature and colonic contents provided a suitable opportunity for the entry of colonic organisms into the bloodstream. This is the presumed mechanism of this patient's attack of bloody diarrhoea and subsequent development of *Clostridium septicum* bacteraemia.

Koransky *et al.*[5] reported an association between *Clostridium septicum* bacteraemia and malignancy. In their review of 21 patients with solid tumours 67% had cancer of the colon and one patient developed cancer of the caecum two years after an episode of *Clostridium septicum* bacteraemia. In our patient no evidence of a gastrointestinal malignancy was found at necropsy; however, he had a history of prostatic adenocarcinoma which was thought to have been cured by transurethral resection. One case has been reported of clostridial bacteraemia associated with adenocarcinoma of the prostate, but that patient had disease metastatic to the abdomen.[6]

Clostridium septicum is a Gram-positive, obligate, anaerobic rod which produces four exotoxins designated alpha, beta, gamma, and delta.[7] The alpha toxin is a lecithinase that produces the fulminant tissue necrosis and small blood vessel thrombosis seen in *Clostridium septicum* infections.[7] The change in iris colour observed in this patient is consistent with tissue necrosis, which was confirmed on pathological examination.

Although the normal human eye has a rich blood supply, it contains several avascular structures, including the outer retina, vitreous, lens, and cornea.[8] Since many of the ocular vessels, including the central retinal artery, lack anastomoses, under pathological conditions the blood supply of the eye can be severely compromised. With these anatomical features in mind, it is understandable that, if a part of the ocular vasculature were interrupted either by a local toxic effect or by a distant embolic phenomenon, then the minimal collateral circulation might not be sufficient to prevent the ischaemic conditions required for the growth of *Clostridium septicum*.

The mechanism of sudden visual loss experienced by this patient almost certainly involves a vascular event. There was no convincing evidence of embolic foci, nor were there any systemic signs of embolisation affecting other organ systems based on necropsy findings. These observations make it unlikely that a distant embolic phenomenon was responsible for the pathology seen. It is more likely that a local ocular event involving clostridial seeding, production of exotoxin, and subsequent vessel thrombosis and tissue destruction accounts for the ocular pathology observed.

Drs Charles M Gluck and Robert P Laurence, of the Penobscot Bay Medical Center, played primary roles in the care of this patient and kindly reviewed the manuscript.

References

1 Leavelle RE. Gas gangrene panophthalmitis. *Arch Ophthalmol* 1955; **53**: 634–42.

2 Frantz JM, Lemp MA, Font RL, Stone R, Eisner E. Acute endogenous panophthalmitis caused by *Clostridium perfringens*. *Am J Ophthalmol* 1974; **78**: 295–303.

3 Insler MS, Karcioglu ZA, Naugle T Jr. *Clostridium septicum* panophthalmitis with systemic complications. *Br J Ophthalmol* 1985; **69**: 774–7.

4 Renton CJ. Nonocclusive intestinal infarction. *Clin Gastroenterol* 1972; **3**: 655–73.

5 Koransky JR, Stargel MD, Dowell VR Jr. *Clostridium septicum* bacteremia. *Am J Med* 1979; **66**: 63–6.

6 Cabrera A, Tsukada Y, Pickren JW. Clostridial gas gangrene and septicemia in malignant disease. *Cancer* 1965; **18**: 800–6.

7 Smith LD. *The pathogenic anaerobic bacteria.* Springfield: Thomas, 1966: 341–432.

8 Wolff E. *Anatomy of the eye and orbit.* 6th ed. London: Lewis, 1968: 146–9, 406–9.

Accepted for publication 20 March 1987.

British Journal of Ophthalmology, 1988, **72**, 386–389

Role of vitrectomy in *Staphylococcus epidermidis* endophthalmitis

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SUMMARY Seventeen patients with endophthalmitis due to coagulase-negative staphylococcus were treated over a nine-year period with vitrectomy, intraocular antibiotics, and systemic steroids and antibiotics. Fifteen patients presented with moderate to severe disease and visual acuities from counting fingers to light perception, while two had acuities of 20/60 and 20/200. A final visual outcome of 20/70 or better was achieved in 13 of 17 eyes (76%). Only one eye lost perception of light secondary to retinal detachment. Therapy including vitrectomy is an effective means of controlling moderate to severe coagulase-negative staphylococcal endophthalmitis and restoring vision.

Coagulase-negative staphylococci are increasingly recognised as pathogenic in postoperative and post-traumatic endophthalmitis.[1-7] Most of these organisms are probably *Staphylococcus epidermidis*, but the classification of these organisms is becoming more sophisticated and it is recognised that coagulase-negative Gram-positive micrococci besides *Staph. epidermidis* may be pathogenic.[3] In the past, however, these were classified in the group *Staph. epidermidis*. In general the results of therapy are better when *Staph. epidermidis* is the infecting organism than when more virulent organisms, especially Gram-negative, are the offending agents. Because virulence may vary within a classification of coagulase-negative organisms, however, general conclusions regarding therapy may be difficult to reach.

O'Day *et al.* presented good results (20/70 in 83%) for management of 18 cases of *Staph. epidermidis* endophthalmitis with topical and systemic antibiotics and steroids, contrasting these with the less favourable results in cases treated by vitrectomy.[2] Bode *et al.* reported a series of 22 eyes treated with intraocular antibiotics; 13 had also undergone vitrectomy. The success rate was 73% achieving vision of 20/60 or better.[5] We report a consecutive series of 17 eyes treated over a nine-year period by vitrectomy, intraocular antibiotics, and systemic steroids and antibiotics.

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Patients and methods

During the nine years from 1976 to 1985, 17 patients were treated at the Emory Clinic for exogenous endophthalmitis due to coagulase-negative staphylococci with therapy which included vitrectomy. Fourteen had undergone prior cataract extraction. Three had postoperative complications (two vitreous wicks and one conjunctival bleb), and one underwent a surgical posterior capsulotomy. Penetrating trauma preceded the infection in two eyes and one case occurred in the postoperative period after trabeculectomy. The onset of the disease 18 months after surgery indicates this was bleb-associated endophthalmitis. In the remaining 16 eyes the onset of symptoms ranged from two to 21 days with a mean of 16·5 days (Table 1). Symptoms were initially mild in half the cases (minor discomfort with blurred vision) with transition to a more acute course characterised by pain and sudden visual deterioration 24 hours to 21 days later. Six patients with milder disease initially responded to topical steroid administration, delaying the diagnosis of endophthalmitis. Patients presenting after 48 hours of symptoms (n=11) tended to have more vitreous clouding and involvement of the posterior vitreous.

Preoperative visual acuities ranged from counting fingers to light perception in 15 cases; the remaining two were 20/60 and 20/200. Vitreous surgery was undertaken promptly after diagnosis. Indications for surgery were moderate to severe intraocular inflam-

Table 1 *Clinical details summarised*

Case	*Event*	*Days from Event to symptoms*	*Days from Symptoms to diagnosis*	*Sequelae*	*Final VA*	*Followup (post-vitrectomy)*
1	ICCE	7	2	—	20/30	7 years
2	ICCE	7	42	—	20/70	6 months
3	ICCE	3	3	—	20/30	2 years
4	ICCE	5	1	—	20/30	4·5 years
5	ICCE	4	1	—	20/70	6 years
6	ICCE Vitreous wick	21	5	CMO	20/400	7 years
7	ICCE	5	1	—	20/30	5 years
8	ICCE Vitreous wick	7	1	RD	NPL	
9	ECCE/IOL	5	42	—	20/60	15 years
10	ECCE/IOL	2	1	RD/ABK	CF	6 months
11	ECCE/IOL	2	4	RD	20/30	6 months
12	ECCE/IOL	3	10	—	20/60	21 months
13	2′ IOL Bleb	540	14	—	20/60	4 years
14	Capsulotomy	2	3	—	20/60	4·5 years
15	Trabeculectomy	4	6	—	20/200	5 years
16	Penetrating trauma	7	4	—	20/25	21 months
17	Penetrating trauma	4	3	—	20/50	9 months

'Event' signifies the surgery or trauma preceding endophthalmitis. ICCE: intracapsular cataract extraction. ECCE: extracapsular cataract extraction. IOL: intraocular lens. 2′ IOL: secondary intraocular lens. CMO: cystoid macular oedema. RD: retinal detachment. ABK: aphakic bullous keratopathy. NPL: no perception of light.

mation with loss of fundus detail on indirect ophthalmoscopy (15 cases), diagnostic difficulty secondary to delayed onset (1), and trauma-associated endophthalmitis (1).

Biopsy material obtained under sterile conditions was immediately inoculated on standard microbiological media and microscopic slides were prepared. Vitrectomy was performed through an anterior limbal approach in nine cases, while eight were operated on by the pars plana. At the conclusion of surgery intraocular antibiotics were injected as follows: gentamicin 100 to 400 μg plus a cephalosporin or loridine 100 μg or methicillin 250 μg. High-dose prednisolone (60 mg) was started 24 hours postoperatively in most cases (15/17) and rapidly tailed. The postoperative regimen included an intravenous cephalosporin or ticarcillin plus topical six-hourly gentamicin (14 mg/ml) and two-hourly prednisolone acetate 1% in most cases.

Results

Visual results were gratifying, with 20/70 or better achieved in 13 of the 17 (76%) patients. In the cases with vision less than 20/70, one was due to pre-existing end-stage glaucoma. Aphakic bullous keratopathy followed retinal detachment in one case, and cystoid macular oedema was present in another, possibly associated with the preoperative vitreous wick. A single case had an inoperable retinal detachment and vision was totally lost (Table 1).

The major complication in these cases was the development of retinal detachment (18%). One detachment occurred in an eye with a vitreous wick and a cyclitic membrane at the time of vitrectomy. Surgical repair was unsuccessful. The remaining two cases were due to presumed entry-site complications. They were successfully repaired, though one had postoperative bullous keratopathy which limited postoperative vision to counting fingers. In this series antibiotic sensitivities of the pathogens cultured were as follows: gentamicin 100% and cephalothin 83%. Where resistance to cephalothin was reported, the organisms were sensitive to methicillin.

Discussion

The management of coagulase-negative staphylococcus endophthalmitis remains controversial, since various forms of therapy are reported to be successful. Unfortunately, reported series may not be comparable owing to differences in the virulence of organisms, severity of the disease at presentation, delay in onset, antibiotic sensitivities, and host response. O'Day *et al.* reported good results from non-invasive therapy, with 83% of patients achieving vision of 20/70 or better.[2] They contrasted their results with those reported in patients treated by vitrectomy. Final vision of 20/70 was achieved in only 42% of these cases. Bode *et al.* reported 22 eyes treated with intraocular antibiotics; 73% achieved 20/60 or better.[5] The condition of these 13 eyes was judged severe, however, and they underwent additional vitrectomy. Vision of 20/60 was achieved in 62% of this subgroup. Our series demonstrates excellent results in eyes treated with vitrectomy, intraocular antibiotics, and systemic steroids and antibiotics. Most eyes in this series had moderate to severe disease and 89% had a vision of counting fingers or less, with obscuration of all fundus detail at the time of surgical intervention.

Early mild disease may respond well to intraocular antibiotic therapy alone without vitreous removal. When the clinical presentation is that of an indolent endophthalmitis, the clinical picture may strongly suggest *Staphylococcus epidermidis*, and such cases may be managed initially without surgical intervention. Confronted with acute endophthalmitis, either moderate or severe, or established disease with severe intraocular inflammation, the clinician cannot always be confident he is dealing with an organism of low virulence which is likely to respond to antibiotic therapy alone. If therapeutic vitrectomy is delayed, pending microbiological diagnosis, the delay may allow progression of intraocular inflammation. The potential therapeutic advantage of surgical vitrectomy may thereby be compromised. Immediate vitrectomy, performed at the time of vitreous biopsy in such cases, has three advantages: (1) living organisms are removed, enhancing control of infection; (2) removal of dead organisms reduces the inflammatory stimulus and consequent inflammatory chorioretinal damage which determines visual outcome; (3) removal of vitreous opacities expedites visual recovery.

When a case of moderate to severe bacterial endophthalmitis presents to our clinic, we concur with the recommendations to obtain a vitreous sample quickly in order to establish a microbiological diagnosis. Since needle aspiration may transmit unacceptable traction to the peripheral retina, we usually prefer to remove the vitreous with a suction-cutting instrument. When performed in this way, the biopsy may be extended to remove a larger amount of vitreous. In the presence of complete posterior vitreous detachment this would not result in traction on inflamed, oedematous retina, and most of the vitreous may be removed with relative safety. Where posterior vitreous detachment has not occurred or is incomplete, limited 'core' vitrectomy would minimise the risk of retinal traction while reducing the inflammatory load and vitreous opacification. There would remain the risk of the late effects of subsequent detachment of the residual vitreous cortex.

The major complication of intraocular surgery in this setting is the development of retinal detachment. Sympathetic ophthalmitis has also been reported.[8] In our series two of the three retinal detachments were successfully repaired. The third detachment could not be repaired and was associated with known preoperative risk factors in the anterior segment, a cyclitic membrane and vitreous wick. Even with these complications, however, only one eye in the series of 17 was ultimately lost, and the final visual results of this series are comparable to reports with antibiotic therapy alone. Vitreous surgery did not compromise the prognosis in these eyes with *Staphylococcus epidermidis* endophthalmitis and provided useful adjunctive therapy in moderate to severe cases. Although systemic antibiotics were administered, we recognise there is no evidence that minimum inhibitory concentrations are achieved in the vitreous by this route.

The role of steroid therapy is to suppress the massive inflammatory infiltration of the choroid and retina which results from intraocular infection. The inflammatory stimulus includes both live and dead organisms. Hence intraocular antibiotics alone will not contain the inflammatory response. Studies to date have not established the optimum route or dose of steroid administration. O'Day *et al.* reported the use of predominantly topical or periocular steroid, while our cases were mostly (15 of 17) treated with systemic steroids.[2] This will need more detailed analysis, relating results to the degree of inflammation and to the different species of coagulase-negative staphylococci.

Staphylococcus epidermidis is widely reported as pathogenic for endophthalmitis.[1-7] Until recently its identification has been based on the coagulase test. Supplementary tests are required to further differentiate coagulase-negative species of staphylococci, since this may have clinical significance. *Staph. haemolyticus*, for example, is coagulase-negative but parallels *Staph. aureus* with respect to virulence and antibiotic sensitivity. More recently Seal *et al.*[4] modified the Baird-Parker scheme both to quantify a number of tests and to apply these specifically to coagulase-negative cocci of ophthalmic importance. There is also evidence that slime production may provide a useful index of pathogenicity.[9] It is important to distinguish between species in order to interpret the results of different types of treatment.

We recommend consideration of vitrectomy in moderate and severe endophthalmitis combined with intraocular antibiotic therapy and systemic steroids. This approach permits adequate vitreous biopsy, reduces the inflammatory stimulus of live and dead bacteria, reduces endotoxin release from more virulent organisms, and clears the visual axis. The results of a surgical approach are not inferior to non-surgical management as previously suggested.

This work was supported in part by a departmental grant from Research to Prevent Blindness, Inc.

References

1 Valenton MJ, Brubaker RF, Allen HF. *Staphylococcus epider-*

midis (albus) endophthalmitis. Report of two cases after cataract extraction. *Arch Ophthalmol* 1973; **89**: 94–6.

2 O'Day DM, Jones DB, Patrinely J, Elliott JH. *Staphylococcus epidermidis* endophthalmitis. Visual outcome following non-invasive therapy. *Ophthalmology* 1982; **89**: 354–60.

3 Packer AJ, Koontz FP. Ocular staphylococcal infections. *Am J Ophthalmol* 1984; **97**: 645.

4 Seal D, Wright P, Badiani D. New ways to classify staphylococci of ophthalmic importance. *Invest Ophthalmol Vis Sci* 1986; **27** (suppl): 88.

5 Bode DD Jr, Gelender H, Forster RK. A retrospective review of endophthalmitis due to coagulase-negative staphylococci. *Br J Ophthalmol* 1985; **69**: 915–9.

6 Puliafito CA, Baker AS, Haaf J, Foster CS. Infectious endophthalmitis. Review of 36 cases. *Ophthalmology* 1982; **89**: 921–9.

7 Weber DJ, Hoffman KL, Thoft RA, Baker AS. Endophthalmitis following intraocular lens implantation: report of 30 cases and review of the literature. *Rev Infect Dis* 1986; **8**: 12–20.

8 Croxatto JO, Galantine P, Cupples HP, Harper D, Reader A, Zimmerman LE. Sympathetic ophthalmia after pars plana vitrectomy-lensectomy for endogenous bacterial endophthalmitis. *Am J Ophthalmol* 1981; **91**: 342–6.

9 Davenport DS, Massanari RM, Pfaller MA, Bale MJ, Streed SA, Hierholzer WJ Jr. Usefulness of a test for slime production as a marker for clinically significant infections with coagulase-negative staphylococci. *J Infect Dis* 1986; **153**: 332–9.

Accepted for publication 20 March 1987.

British Journal of Ophthalmology, 1988, 72, 390–393

α_1-Antitrypsin and serum albumin in tear fluids in acute adenovirus conjunctivitis

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SUMMARY The α_1-antitrypsin and serum albumin levels in tear fluids were measured by electroimmunodiffusion in 76 healthy subjects and 63 patients with acute adenovirus conjunctivitis. They were found to be significantly increased during the acute phase of the disease. There was a correlation between increased severity of disease and increased levels of both the proteins. There was no significant difference in the tear α_1-antitrypsin and serum albumin levels in viral isolation-positive and isolation-negative patients. The raised levels of the two proteins in tears may reflect conjunctival inflammation rather than infection, since both isolation-positive and isolation-negative patients had the raised levels. The levels of the two proteins returned to normal with clinical improvement.

α_1-antitrypsin controls the activity of diverse proteolytic enzymes.[1] It is found in tears, saliva, perilymph, bile, synovial fluid, and amniotic fluid.[2-5] It plays a significant part in regulating the immune response by inhibiting the transformation and migration of lymphocytes.[6] Its role in corneal ulcer and other corneal diseases has been studied.[7-9] However, only a few limited studies are available on its level in patients with conjunctival disease.[7 9 10]

The levels of tear immunoglobulin,[11] serum immunoglobulin,[11] complement component,[12] and tear lysozyme[13] have been reported by us in patients with acute adenovirus conjunctivitis. Here we report our observations on tear α_1-antitrypsin level in this disease. Serum albumin levels in tear fluids have been measured because they indicate leakage of serum proteins into tears. The findings on adenovirus culture have been described elsewhere.[14]

Material and methods

The present study was carried out among 76 healthy subjects and 63 patients with clinically diagnosed acute adenovirus conjunctivitis attending the outpatient department of Guru Nanak Eye Centre, New Delhi. The control group comprised healthy subjects who had no evidence of ocular or systemic disease and who attended the Eye Centre mainly for the purpose of refraction. In the control group were 40 males and 36 females with a mean age of 35·7 (SD 17·6) years (range 8 to 60 years), and the diseased group comprised 48 males and 15 females with mean age of 30·9 (SD 11·7) years (range 5 to 63 years). The diagnosis of acute adenovirus conjunctivitis was established by detailed clinical examination including slit-lamp biomicroscopy, bacterial culture, and viral culture.

Clinically the patients presented with sudden onset of unilateral or bilateral pain, redness, and watery discharge with no visual deterioration. Ocular examination showed lid oedema, conjunctival congestion, and chemosis of bulbar conjunctiva, with frequent subconjunctival haemorrhages. There was no corneal involvement in any patient as confirmed by fluorescein staining and subsequent slit-lamp examination with cobalt blue filter.

The patients were subgrouped as mild or severe according to the clinical presentation. The patients with mild conjunctivitis had minimal lid oedema, conjunctival congestion, and no subconjunctival haemorrhage or chemosis of the bulbar conjunctiva. However, patients with severe conjunctivitis had moderate lid oedema, extensive conjunctival congestion, and chemosis of bulbar conjunctiva and subconjunctival haemorrhage. All such patients who showed any positive bacterial culture were excluded from the study.

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Specific tests adopted for the identification of adenovirus were: haemagglutination, haemagglutination inhibition, haemadsorption, complement fixation test, and serum inhibitory titre against adenovirus.[14,15] The reference standard antigen and the antisera were obtained from the National Institutes of Health, Bethesda, USA. The typing of adenovirus was done by the numbering system proposed by Norrby.[16] Adenovirus types 2, 7, or 8 could be cultured from only 26 out of 63 patients.[13]

Tear samples were also collected for α_1-antitrypsin and serum albumin measurements from 41 patients during the remission stage, when there was no clinical evidence of conjunctivitis.

Stimulated tear samples (100 to 200 µl) were collected by the method described previously[17] and stored at −20°C until assayed. The α_1-antitrypsin and serum albumin levels in tear fluid samples were quantified by electroimmunodiffusion.[18] Monospecific goat antihuman α_1-antitrypsin and antihuman serum albumin sera and their respective reference standards were obtained from Meloy Laboratories, Virgina, USA. The levels of the two proteins in tear fluids were calculated from the calibration curve constructed by incorporating three known concentrations of the reference standards for every set of determinations. The results were statistically analysed by Student's *t* test.

Results

The α_1-antitrypsin and serum albumin levels in tear fluids in patients with clinically diagnosed acute adenovirus conjunctivitis and healthy controls are given in Table 1. The mean α_1-antitrypsin level in healthy controls was 12·1 mg/l. The mean levels in patients with acute adenovirus conjunctivitis was 47·8 mg/l for α_1-antitrypsin and 144·5 mg/l for serum albumin in tear fluids. There was a statistically significant difference when the tear α_1-antitrypsin ($p<0{\cdot}001$) and serum albumin ($p<0{\cdot}001$) levels in the patients with conjunctivitis were compared with the respective levels in healthy controls. The tear α_1-antitrypsin levels in healthy controls were 4·4 mg/l in males and 4·0 mg/l in females, and the difference in the two sexes was not statistically significant ($p<0{\cdot}50$). Similarly serum albumin levels in tear fluids was 11·5 mg/l in males and 12·7 mg/l in females, and the difference in the two sexes was not statistically significant ($p>0{\cdot}40$). In the patients with acute adenovirus conjunctivitis there was no significant difference ($p>0{\cdot}50$) when the tear α_1-antitrypsin level in males (45·3 mg/l) and females (50·3 mg/l) were compared. Similarly when the serum albumin levels in tear fluids in patients with conjunctivitis in males (141·2 mg/l) and females (151·7 mg/l) were compared, there was no significant difference ($p>0{\cdot}60$).

Table 1 α_1-*Antitrypsin and serum albumin in tear fluids in healthy subjects and patients with acute adenovirus conjunctivitis (mg/l)*

	No. of cases	α_1-*Antitrypsin*		*Serum albumin*	
		Mean±SD	*Range*	*Mean±SD*	*Range*
Healthy subjects	76	4·2±2·2	1·0–10·0	12·1±5·5	1·6–24·0
Male	40	4·4±2·2	1·0–10·0	11·5±6·0	1·6–24·0
Female	36	4·0±2·1	1·0–8·8	12·7±5·0	2·1–20·4
Conjunctivitis	63	48·0±26·9	10·2–97·4	144·5±62·1	18·6–206·8
Male	29	45·3±28·4	10·8–81·7	141·2±63·7	29·4–206·8
Female	34	50·3±25·8	10·2–97·4	151·7±58·8	18·6–206·8

Table 2 shows the tear α_1-antitrypsin and serum albumin levels in mild and severe stages of clinically diagnosed acute adenovirus conjunctivitis. There were significant increases ($p<0{\cdot}001$) in comparison with the respective levels in healthy controls both in mild and in severe stages for α_1-antitrypsin and serum albumin levels in tear fluids.

The tear α_1-antitrypsin and serum albumin levels in viral isolation-positive and viral isolation-negative patients are given in Table 3. There was a statistically significant increase ($p<0{\cdot}001$) in tear α_1-antitrypsin levels when the levels in healthy controls were compared with the levels both in viral isolation-positive and viral isolation-negative patients. However, there was no statistically significant difference ($p>0{\cdot}20$) between the tear α_1-antitrypsin level

Table 2 α_1-*Antitrypsin and serum albumin levels in tear fluids in mg/l in mild and severe stages of acute adenovirus conjunctivitis*

	No. of cases	α_1-*Antitrypsin*		*Serum albumin*	
		Mean±SD	*Range*	*Mean±SD*	*Range*
Mild	25	19·4±8·0	10·2–41·0	85·6±60·5	18·6–171·5
Severe	38	66·8±16·0	28·5–97·4	183·2±14·2	141·5–206·8

Table 3 α_1-*Antitrypsin and serum albumin in tear fluids in mg/l in the acute phase in viral isolation-positive and viral isolation-negative patients with acute adenovirus conjunctivitis*

	No. of cases	α_1-*Antitrypsin*		*Serum albumin*	
		Mean±SD	*Range*	*Mean±SD*	*Range*
Isolation-positive	26	53·7±25·4	15·8–97·4	134·9±71·8	18·6–196·8
Isolation-negative	37	44·0±27·5	10·2–89·3	151·2±54·2	29·4–206·8

Table 4 *α_1-Antitrypsin and serum albumin in tear fluids in mg/l in the acute and remission stages of acute adenovirus conjunctivitis*

	No. of cases	*α_1-Antitrypsin*		*Serum albumin*	
		Mean±SD	*Range*	*Mean±SD*	*Range*
Acute	41	42·9±26·1	11·9–80·9	141·9±63·3	22·7–206·8
Remission	41	4·8±1·7	1·7–8·8	12·9±5·2	7·0–34·0

in viral isolation-positive patients (53·7 mg/l) and viral isolation-negative patients (44·0 mg/l). Similar results were observed in respect of serum albumin levels in tear fluids in viral isolation-negative and viral isolation-positive patients.

The tear α_1-antitrypsin levels were measured in 41 patients during the acute and remission stages (Table 4). The mean level during the acute stage was 42·9 mg/l which decreased to 4·8 mg/l during the remission stage. There was a statistically significant difference ($p<0·001$) between the levels in the acute and remission stages. However, there was no significant difference ($p>0·20$) between the tear α_1-antitrypsin levels in healthy subjects and in the remission stage. Similarly the level of serum albumin in tear fluids during the acute phase was 141·9 mg/l and it decreased to 12·9 mg/l during the remission stage. There was no statistically significant difference ($p>0·50$) between the level of serum albumin in tear fluids in healthy controls and in the remission stage.

Discussion

Serum α_1-antitrypsin is frequently increased in malignancy,[19] acute infections,[20] corticosteroid therapy,[21] rheumatoid arthritis,[22] pregnancy,[23] oestrogen therapy,[24] sarcoidosis,[25] leprosy,[26] and uveitis.[27] There is good evidence that α_1-antitrypsin is involved in the regulation of the immune system.[6] There are a few studies on the study of tear α_1-antitrypsin levels in various ocular conditions. Bacterial infections of the conjunctiva and cornea cause an increase of α_1-antitrypsin level, and the measurement of its level may help in the diagnosis of ocular inflammation.[10] It has also been shown that tear α_1-antitrypsin levels may rise in inflamed eyes in the absence of corneal involvement, for example, in cases of rosacea keratitis and allergic conjunctivitis.[7,9] In fact in cases of allergic conjunctivitis tear levels of both α_1-antitrypsin and serum albumin were observed to approach serum levels rapidly, indicating a direct leak from inflamed vessels.[7]

The tear α_1-antitrypsin level in healthy controls in the present study are comparable to the levels reported by others.[7-9] We have measured the levels in the patients with clinically diagnosed acute adenovirus conjunctivitis in an attempt to determine the relationship, if any, between conjunctival inflammation per se and tear α_1-antitrypsin levels.

A remarkable increase in α_1-antitrypsin and serum albumin was observed in tear fluids from inflamed eyes with acute adenovirus conjunctivitis. There is general agreement between the extent of conjunctival inflammation and the levels of the two proteins in tear fluids (Table 2). The levels of the two proteins in tear fluids during the remission stage fell to those found in healthy controls. It is therefore likely that the high levels of α_1-antitrypsin and serum albumin in tear fluids in patients with acute adenovirus conjunctivitis were due to the inflammation and not inherent or pre-existent.

The origin of the proteins in tear fluids is not clear. Active transport, transudation from serum, local production, or some combination of these factors may be involved. The route(s) by which increased amounts of α_1-antitrypsin enters tears in eyes inflamed from acute adenovirus conjunctivitis is unknown. The most likely explanation is that the α_1-antitrypsin and serum albumin leak passively from blood vessels that supply inflamed eyes. In support of this interpretation is the observation that the ratio of serum albumin to α_1-antitrypsin is the same in tear fluids from conjunctivitis patients with raised α_1-antitrypsin levels as in healthy controls.

α_1-Antitrypsin acts like an acute-phase reactant, and its level tends to rise in inflammatory conditions.[28] It has been commented that because of the acute reactant nature its concentration may change dramatically in the presence of inflammation.[1] The protease inhibitor may also have a protective function.[26] It has been suggested that during infection α_1-antitrypsin production increases to counteract endogenous or exogenous protease.[29,30] It is possible that there is an excessive load of proteases in tears in acute adenovirus conjunctivitis which may be counterbalanced by the release of α_1-antitrypsin.

The raised α_1-antitrypsin and serum albumin in tear fluids in patients with acute adenovirus conjunctivitis in the present study are probably an indicator of inflammation rather than infection, because the levels of the two proteins were markedly high in viral isolation-positive and viral isolation-negative patients. It will be interesting to study the level of these two proteins in other inflammatory diseases of the cornea and conjunctiva.

Thanks are due to Dr A K Prasad, Head of the Respiratory Virology Department, Vallabhbhai Patel Chest Institute, New Delhi, for help in viral culture studies.

References

1 Morse JO. Alpha-1 antitrypsin deficiency. *N Engl J Med* 1978; **299**: 1045–8.

2 Chevance LG, Causse JR, Berges J. Alpha-1 antitrypsin activity of the perilymph. Occurrence during progression of otospongiosis. *Arch Otolaryngol* 1976; **102:** 363–4.

3 Kyay-Myint TO, Howell AM, Murphy GM. Alpha-1 antitrypsin in duodenal fluid and gall bladder bile. *Clin Chim Acta* 1975; **59:** 51–4.

4 Talamo RC. Basic and clinical aspects of the alpha-1 antitrypsin. *Pediatrics* 1975; **56:** 91–9.

5 Sharp HL. The current status of alpha-1 antitrypsin, a protease inhibitor in gastrointestinal diseases. *Gastroenterology* 1973; **70:** 611–21.

6 Arora PK, Miller HC, Aronson LD. Alpha-1 antitrypsin is an effector of immunologic stasis. *Nature* 1978; **274:** 589–90.

7 Berman MB, Barber JC, Talamo RC, Langley CE. Corneal ulceration and the serum antiproteases. I. alpha-1 antitrypsin. *Invest Ophthalmol Vis Sci* 1973; **12:** 759–70.

8 Prause JU. Serum albumin, serum antiproteases and polymorphonuclear leucocyte neutral collagenolytic protease in the tear fluid of patients with corneal ulcer. *Acta Ophthalmol (Kbh)* 1983; **61:** 272–82.

9 Sen DK, Sarin GS. Tear and serum alpha-antitrypsin levels in corneal and conjunctival diseases. In: Holly FJ, ed. *The preocular tear film in health, disease and contact lens wear.* Texas: Lubbock, Dry Eye Institute, 1986: 192–9.

10 Zirm M, Ritzinger I. The diagnostic and prognostic value of alpha-1 antitrypsin measurement in tear fluids. *Klin Monatsbl Augenheilkd* 1978; **173:** 221–5.

11 Gupta AK, Sarin GS. Serum and tear immunoglobulin levels in acute adenovirus conjunctivitis. *Br J Ophthalmol* 1983; **67:** 195–8.

12 Gupta AK, Sarin GS. Serum complement component depression during acute adenovirus conjunctivitis. *Br J Ophthalmol* 1984; **68:** 350–2.

13 Gupta AK, Sarin GS, Lamba PA, D'Souza P. Immunoassay of tear lysozyme in acute adenovirus conjunctivitis. *Br J Ophthalmol* 1986; **70:** 439–41.

14 Gupta AK, Prasad AK. Epidemic acute conjunctivitis in Delhi (1981): a virological study. *Afro-Asian J Ophthalmol* 1982; **1:** 62–5.

15 Busy DWG, House W, MacDonald JR. *Virological techniques.* London Churchill, 1964: 136.

16 Norrby E. The structural and functional diversity of adenovirus capsid components. *J Gen Virol* 1969; **5:** 221–36.

17 Sen DK, Sarin GS, Mani K, Saha K. Immunoglobulin in tears of normal Indian people. *Br J Ophthalmol* 1976; **60:** 302–4.

18 Talamo RC, Langley CE, Hyslop NE Jr. A comparison of functional and immunochemical measurement of serum alpha-1 antitrypsin, in Pulmonary Emphysema and Proteolysis. In: Mittman C, ed. *Pulmonary emphysema and proteolysis.* New York: Academic Press, 1972.

19 Clark DG, Clifton EE, Newton BL. Antiproteolytic activity of human serum with particular reference to its changes in the presence and consideration of its use for detection of malignant neoplasia. *Proc Soc Exp Biol Med* 1948; **69:** 276–83.

20 Jacobsson K. Studies on the determination of fibrinogen in human blood plasma in studies on trypsin and plasmin inhibitors in human blood serum. *Scand J Clin Lab Invest* 1955; **14** (suppl): 57–102.

21 Faarvang HJ, Lauritsen OS. Relationship between serum concentration and urinary output of trypsin inhibitor after cortisone administration. *Scand J Clin Lab Invest* 1963; **15:** 483–90.

22 Cleve H, Behrend T. Quantitative immunological determination of alpha-1 acid glycoprotein and alpha-1 antitrypsin in the sera of patients with rheumatoid arthritis. *Z Rheumatol* 1966; **25:** 278–83.

23 Ganrot PO, Bjerre B. Alpha-1 antitrypsin and alpha-2 macroglobulin concentration in serum during pregnancy. *Acta Obstet Gynecol Scand* 1967; **46:** 126–37.

24 Schumacher GFB, Pearl MJ. Alpha-1 antitrypsin in cervical mucus. *Fertil Steril* 1968; **19:** 91–9.

25 Young C Jr, Headings VE, Bose S, Harden KA, Crockett ED Jr, Hackney RL Jr. Apha-1 antitrypsin level in sarcoidosis: relationship to disease activity. *Chest* 1973; **64:** 39–45.

26 Agarwal SK, Saha K. Serum alpha-1 antitrypsin in various forms of leprosy. *Ind J Med Res* 1978; **68:** 136–9.

27 Gupta AK, Sarin GS. Immunoassay of serum alpha-1 antitrypsin level in uveitis. *Br J Ophthalmol* 1984; **68:** 242–4.

28 Sharp HL. Alpha-1 antitrypsin deficiency and liver diseases. In: Read AE, ed. *Modern trends in gastroenterology.* 5th ed. London: Butterworths, 1975: 140.

29 Herman G, Miesscher PA. Differentiation of leucocyte fibrinolytic enzymes from plasmin by the use of plasmatic proteolytic inhibitors. *Int Arch Allergy* 1965; **27:** 34–41.

30 Ohlsson K. Interaction between human or dog leucocyte proteases and plasma protease inhibitors. *Scand J Clin Lab Invest* 1971; **28:** 225–30.

Accepted for publication 25 March 1987.

British Journal of Ophthalmology, 1988, **72**, 394–398

Origin of disc new vessels assessed by videofluorography*

N A JACOBS, C A STEELE, AND K B MILLS

From Manchester Royal Eye Hospital, Manchester

SUMMARY Ten patients with disc neovascularisation of various aetiologies were studied to ascertain the origin of their new vessels. Fluorescein angiography was carried out with an image intensified video camera. A retinal artery derivation was demonstrated for the first time and was seen in three cases. Six further patients showed a retinal venous supply, and finally there was one from a choroidal source.

The formation of retinal new vessels in response to ocular ischaemic[1] of inflammatory[2] disease is well recognised. In 1948 Michaelson[3] stated that new vessels are associated nearly always with retinal veins. Henkind[1] concurred that retinal new vessels arise generally from veins and rarely from arteries. Regarding disc neovascularisation, he noted that, apart from a retinal origin of the vessels, a ciliary origin exists in certain cases. Asdourian and associates[4] as well as Kohner *et al.*[5] have confirmed a choroidal or posterior ciliary derivation of new vessels from the disc in some instances.

This investigation was designed to identify the source of disc neovascularisation. A videofluorescein angiographic technique similar to that described by Haining[6] was employed.

Materials and methods

Ten patients with significant disc neovascularisation of varying aetiologies were included (Table 1). Because the equipment was available for only a short period suitable patients such as could be found were collected in advance. There were seven diabetics, two cases of chronic ocular ischaemia associated with carotid artery obstruction, and one of unknown inflammatory aetiology with peripheral vascular sheathing. All gave their informed consent.

The Topcon TRC 50VT variable angle retinal camera was used. A Visual Contact 590 Newvicon tube video camera with a microchannel plate image intensifier was attached. Recordings were made with a Sony U-matic tape machine after intravenous injection with 2·5 ml of 25% fluorescein sodium dye.

Results

The recordings obtained were initially slowed to one-quarter of real time by the technical services division of New Scotland Yard. Subsequent assessment was carried out in the audiovisual department at Charing Cross Hospital, where editing facilities allowed infinite adjustment of playback rate. Picture quality was satisfactory in view of the low operating light levels of 10^{-2} to 10^{-3} lux. Resolution under these conditions was about 300 pixels horizontally and 225

Table 1 *Summary of the cases with their disc new vessel origin*

Case no.	*Age*	*Eye*	*VA*	*Origin of disc new vessels*	*Aetiology*
1	44	L	6/6	Retinal vein (Fig. 1)	IDD† 20 years
2	48	L	6/24	Retinal vein	IDD 21 years
3	47	L	6/12	Retinal vein	IDD 36 years
4	62	R	6/9	Retinal vein	Chronic ocular ischaemia
5	77	R	6/12	Retinal vein	Chronic ocular ischaemia
6*	58	R	6/5	Retinal vein	Inflammatory vasculitis
7	65	R	6/24	Retinal artery (Fig. 2)	IDD 18 months
8	36	L	6/9	Retinal artery	IDD 17 years
9	54	L	6/12	Retinal artery	IDD 24 years
10	42	R	6/9	Choroidal (Fig. 3)	IDD 20 years

*No photocoagulation treatment given.
†Insulin dependent diabetes.

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*This paper was given under another title and in a different form at the Eighth International Symposium on Microsurgical Anastomoses for Cerebral Ischaemia in Florence on 14–17 September 1986.

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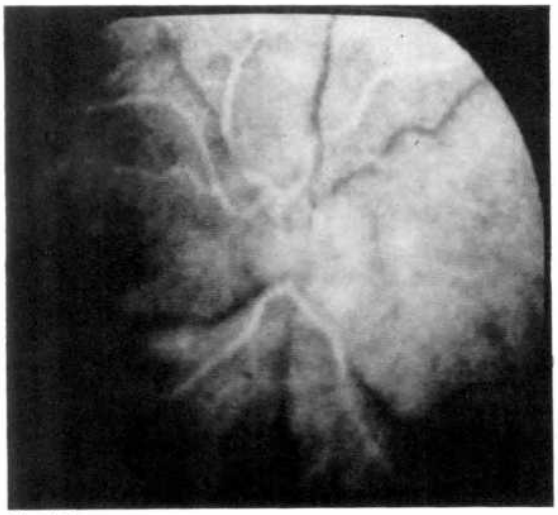

Fig. 1A

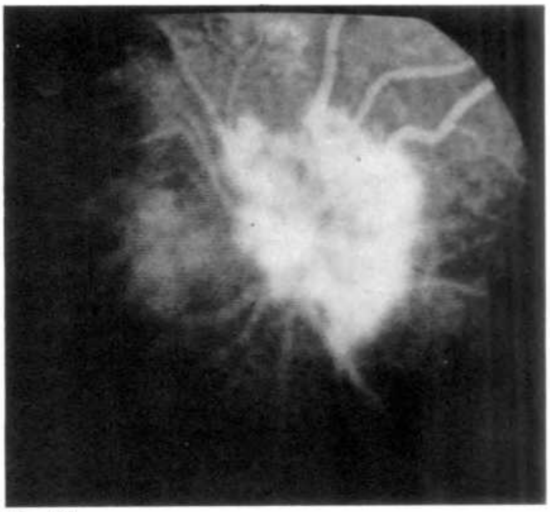

Fig. 1C

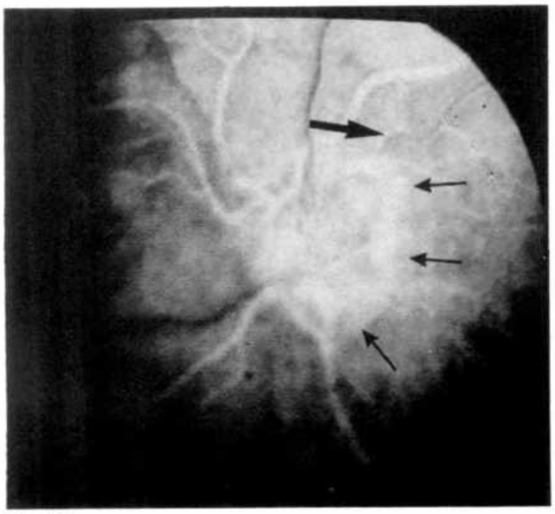

Fig. 1B

Fig. 1 *Videofluorographic stills showing new vessel origin from the retinal vein in the left eye of case 1.* (A) *Late arterial phase before filling.* (B) *Early fluorescence of net (small arrows) and onset of venous lamellar phase in superotemporal branch (large arrow).* (C) *Late venous phase and complete new vessel fluorescence.*

vertically, being approximately half the maximum ideally attainable by the video camera.

A majority of six patients had a new vessel supply derived from the retinal venous circulation. Filling began coincidentally with the onset of venous lamellar flow at the disc (Figs. 1A, B, C). This group comprised three diabetics, both cases of chronic ocular ischaemia, and the case of inflammatory aetiology. Next were three further diabetics, all showing the filling of new vessels simultaneously with the branches of the central retinal artery (Figs. 2A, B, C). Finally, one diabetic showed filling of new vessels synchronously with two cilioretinal arteries (Figs. 3A, B, C).

Discussion

Ocular neovascularisation is mediated by a vasoformative substance, as first proposed by Michaelson.[3] Recent work[7] has brought the identification of such a substance tantalisingly close. However, there are proponents of other concepts, from the mechanical[8] to the Darwinian.[9] The optic disc is a frequent site of neovascularisation in diabetic eye disease.[10] Absence of both the anatomical and fuctional blood-retinal barrier[11] at this site might be relevant. Though a through flow of ocular fluid into the optic nerve head has been demonstrated only in rabbits,[12,13] there is indirect evidence of this phenomenon in primates.[11,14] If it does exist, vessels related to the disc would be exposed to a greater concentration of vasoformative substance than elsewhere.

Shimizu *et al.*[15] have related the degree of retinal ischaemia to the site of new vessel formation. Thus ischaemia was moderate with retinal new vessels only, more severe with disc new vessels, and was seen to be profound with rubeosis. Interestingly, they observed that retinal new vessels were smaller when disc new vessels coexisted, and that in turn disc new vessels were small and retinal new vessels almost absent when associated with rubeosis. This appears to tally with the interpretation placed by Ashton[16] on a study of central retinal vein occlusion carried out by

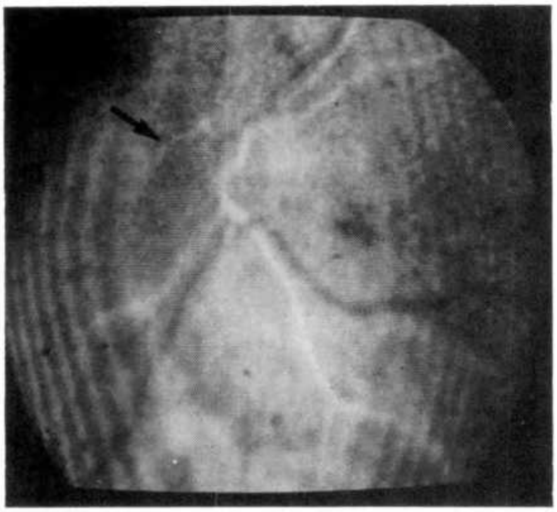

Fig. 2A

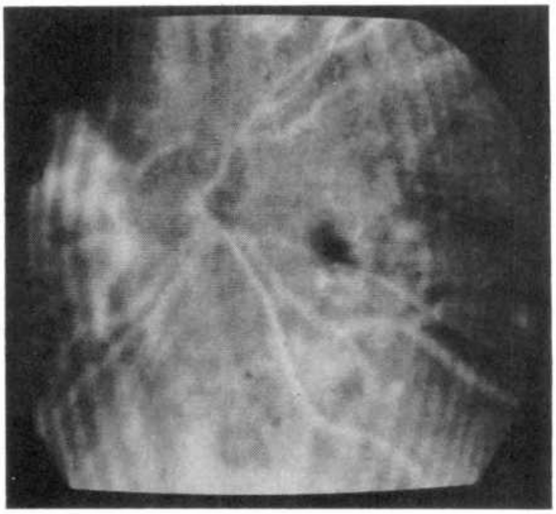

Fig. 2C

Fig. 2 *Videofluorographic stills showing new vessel origin from the retinal artery in the right eye of case 7.* (A) *Early arterial phase with filling of new vessel net feeder (arrow).* (B) *Full arterial phase with outline of net area (arrows).* (C) *Full venous phase and complete new vessel fluorescence.*

Smith[17] prior to the advent of fluorescein angiography —namely, that new vessels, as well as being a passive response to the presence of vasoformative substance, also actively remove this factor from the eye by a process of dialysis. Therefore their presence on the disc would tend to prevent sufficient quantities of vasoformative substance from reaching the drainage angle to provoke rubeosis, and vice versa.

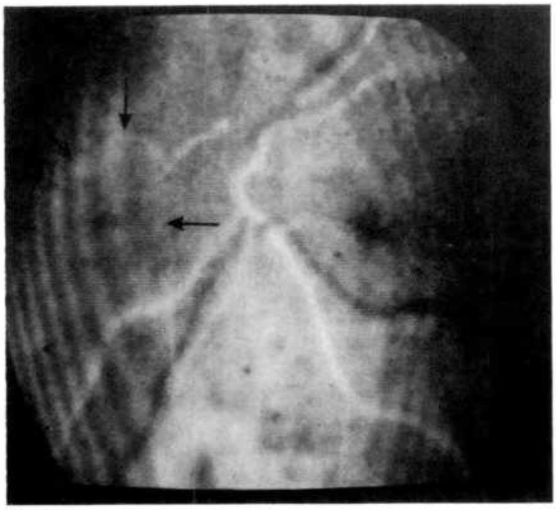

Fig. 2B

For a fluorescein study to yield information useful in a report such as this, recording must begin prior to the arrival of dye and contain as much sequential information as possible. Thus ordinary sequence photography is severely limited by the rate of flash recharge. A cinematographic approach at the normal rate of 26 frames per second or above would be valuable, but there are practical difficulties.[6] Video fluoroscopy with a rate of 25 frames per second is both documented and practicable,[6] especially with the availability of sophisticated technology for analysis. Its feasibility was demonstrated on a normal volunteer. Cilioretinal filling was well displayed, and nasal branches of the central retinal artery were seen to fill before the temporal branches.

A retinal artery derivation of disc new vessels has not been reported previously. Three patients showed this, suggesting that it may be a common occurrence (Fig. 2). With normal angiographic methods it would be difficult to differentiate a uveal from a retinal arterial supply. Retinal venous filling of disc new vessels is well recognised[1 3] and was seen in six of the patients in this study. Although such late angiographic filling may be explained by an epipapillary capillary origin, we discount this possibility for two reasons. First, the new vessel filling coincided in each case with the lamellar venous filling of retinal veins at the disc. Secondly, in two cases (1 and 5) where neovascular complexes were especially large, filling proceeded rapidly in the absence of discernible peripapillary arteriovenous shunts (Fig. 1). Finally, one patient showed a choroidal origin of disc new vessels (Fig. 3). Using rapid sequence angiography, Asdourian and associates[4] described such a choroidal origin in four diabetics and in one patient with carotid

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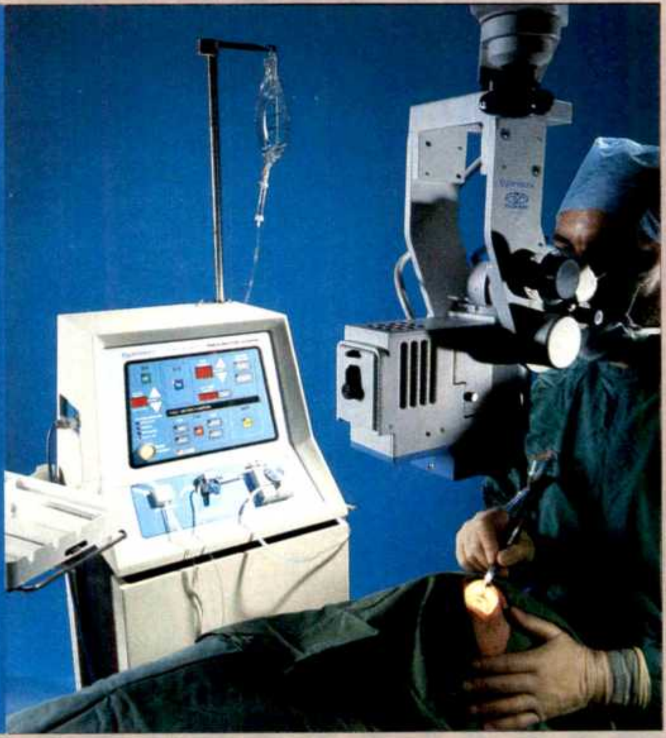

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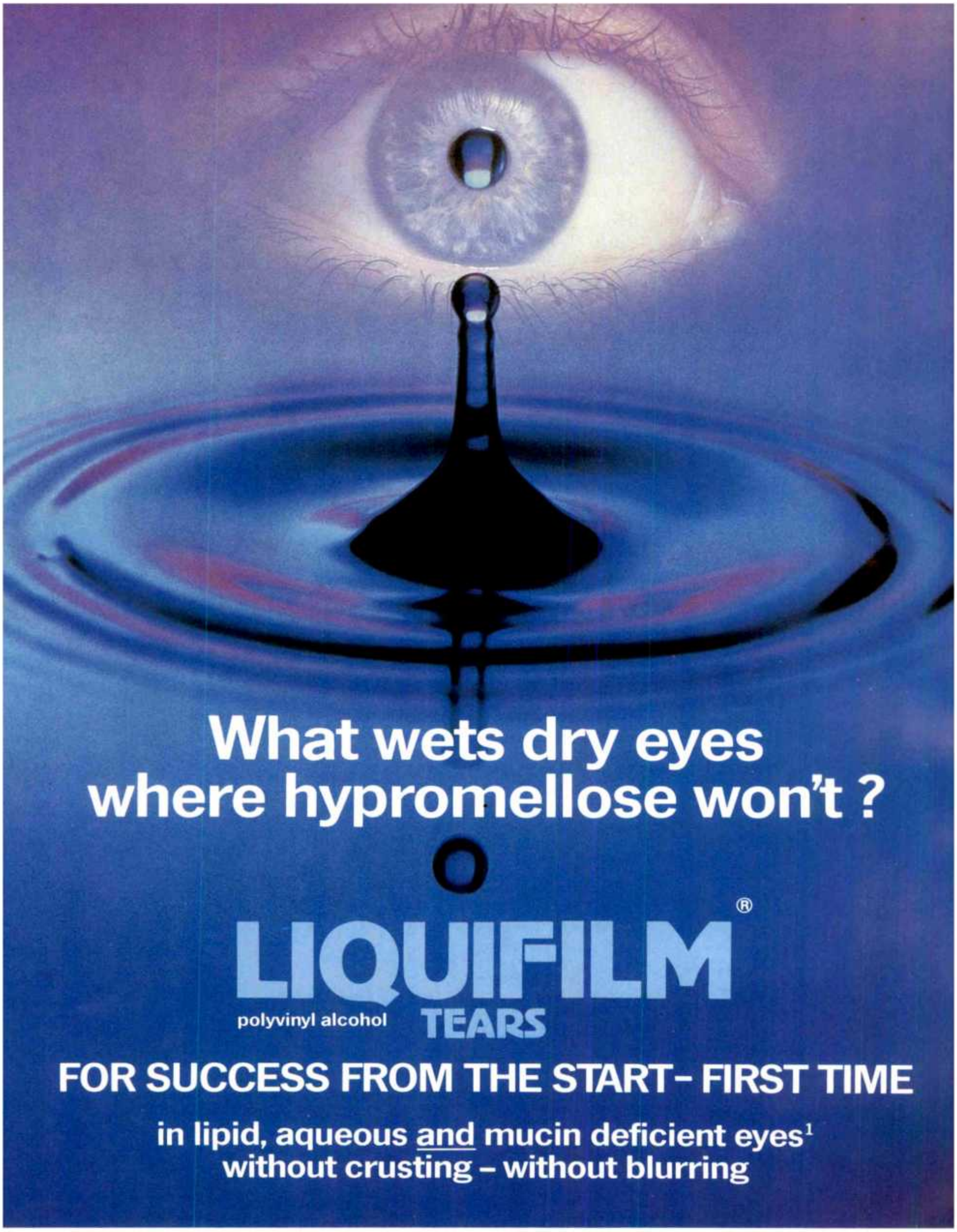
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Reference 1. Kralian LM, American Journal of Optometry and Physiological Optics 1986; **63** (No. 4): 304-308.

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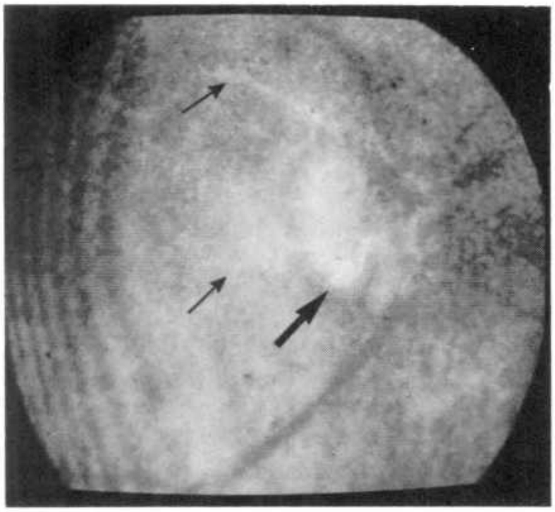


Fig. 3A

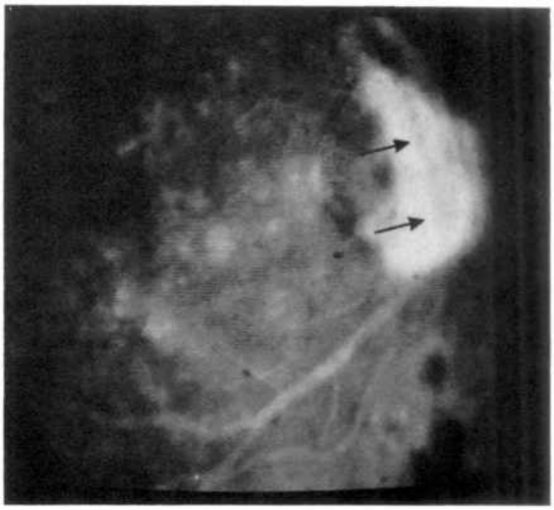


Fig. 3C

Fig. 3 *Videofluorographic stills showing new vessel origin from the choroid in the right eye of case 10.* (A) *Background choroidal phase with two cilioretinal arteries (small arrows) and large new vessel stalk (large arrow).* (B) *Very early arterial phase with enhancement of earlier features.* (C) *Full venous phase with fluorescence of neovascular complex periphery and filling of intervening channels marked by a vertical line moving posteriorly towards the disc (arrows).*

insufficiency. The Japanese work described above,[15] along with an earlier study[18] from the same department, led those authors to conclude that disc new vessels invariably have a choroidal origin. Again, standard fluorescein angiographic techniques were employed.

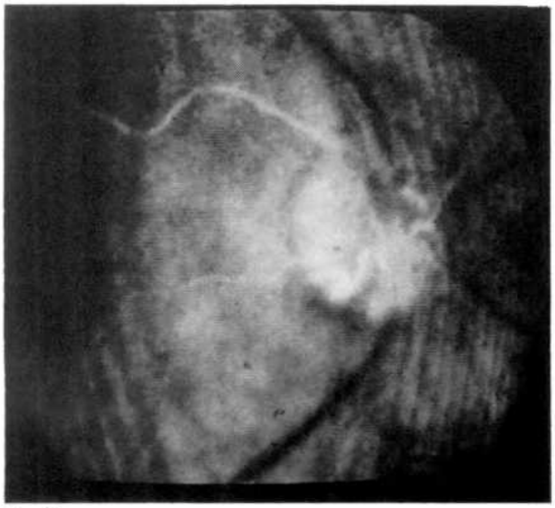


Fig. 3B

Whether any clinical significance may be attached to the disc new vessel origin is unknown. Perhaps this knowledge could indicate the likely response to treatment. It is usually supposed that photocoagulation destroys a proportion of viable retinal tissue, allowing improved oxygenation of the remainder and thereby removing the stimulus for the release of angiogenic substance. Even though the presumably oxygen-rich outer retina is selectively damaged, this treatment may lead to a greater oxygen tension for the inner retina.[3] This supposition is by no means proved, and other possibilities exist. Photocoagulation is known[19] to alter the permeability of the blood retinal barrier, and may allow a leakage of angiogenic substance into the choroid. In that case disc new vessels originating from the choroid might be expected to respond poorly, since leaking angiogenic factor could continue to act as a stimulus. Other work[20] has revealed an important inhibitory role of the pigment epithelium in neovascularisation. Alteration of the normal cell layer population has been shown to increase this inhibitory activity. Perhaps treatment alters the pigment epithelial cells in this way. Whichever mechanism is at work, disc new vessels with an arterial origin may prove most likely to bleed, and would therefore be best excluded from methods of photocoagulation involving occlusion by direct application.

Notwithstanding aetiological and therapeutic conjecture, disc new vessels may be derived from the retinal artery, the retinal vein, or the choroid.

References

1 Henkind P. Ocular neovascularisation—the Krill Memorial Lecture. *Am J Ophthalmol* 1978; **85:** 287–301.

2 Shorb SR, Irvine AR, Kimura SJ, Morris BW. Optic disc neovascularisation associated with chronic uveitis. *Am J Ophthalmol* 1976; **82:** 175–8.

3 Patz A. Retinal neovascularisation: early contributions of Professor Michaelson and recent observations. *Br J Ophthalmol* 1984; **68:** 42–6.

4 Asdourian GK, Goldberg MF, Busse B. Optic disc neovascularisation of uveal (choroidal or posterior ciliary) origin. *Arch Ophthalmol* 1977; **95:** 998–1003.

5 Kohner EM, McLeod D, Marshall J. Diabetic eye disease. In: Keen H, Jarrett J, eds. *Complications of diabetes*. London: Arnold, 1982: 51.

6 Haining WM. Video funduscopy and fluoroscopy. *Br J Ophthalmol* 1981; **65:** 702–6.

7 Taylor CM, Weiss JB, Kissun RD, Garner A. Effect of oxygen tension on the quantities of procollagenase-activating angiogenic factor present in the developing kitten retina. *Br J Ophthalmol* 1986; **70:** 162–5.

8 Stefansson E, Landers MB, Wolbarsht ML. Oxgenation and vasodilatation in relation to diabetic and other proliferative retinopathies. *Ophthalmic Surg* 1983; **14:** 209–26.

9 Cassel GH, Groden LR. New thoughts on ocular neovascularisation: a neurally controlled regenerative process? *Ann Ophthalmol* 1984; **16:** 138–41.

10 Taylor E, Dobree JH. Proliferative diabetic retinopathy—site and size of initial lesions. *Br J Ophthalmol* 1970; **54:** 11–8.

11 Tso MOM, Shih C-Y, McLean IW. Is there a blood-brain barrier at the optic nerve head? *Arch Ophthalmol* 1975; **93:** 815–25.

12 Fowlks WL. Meridional flow from the corona ciliaris through the pararetinal zone of the rabbit vitreous. *Invest Ophthalmol Vis Sci* 1963; **2:** 63–71.

13 Hayreh SS. Posterior drainage of the intraocular fluid from the vitreous. *Exp Eye Res* 1966; **5:** 123–44.

14 Peyman GA, Apple D. Peroxidase diffusion processes in the optic nerve. *Arch Ophthalmol* 1972; **88:** 650–4.

15 Shimizu K, Kobayashi Y, Muraoka K. Midperipheral fundus involvement in diabetic retinopathy. *Ophthalmology* 1981; **88:** 601–11.

16 Ashton N. Neovascularisation in Ocular Disease. *Trans Ophthalmol Soc UK* 1961; **81:** 145–61.

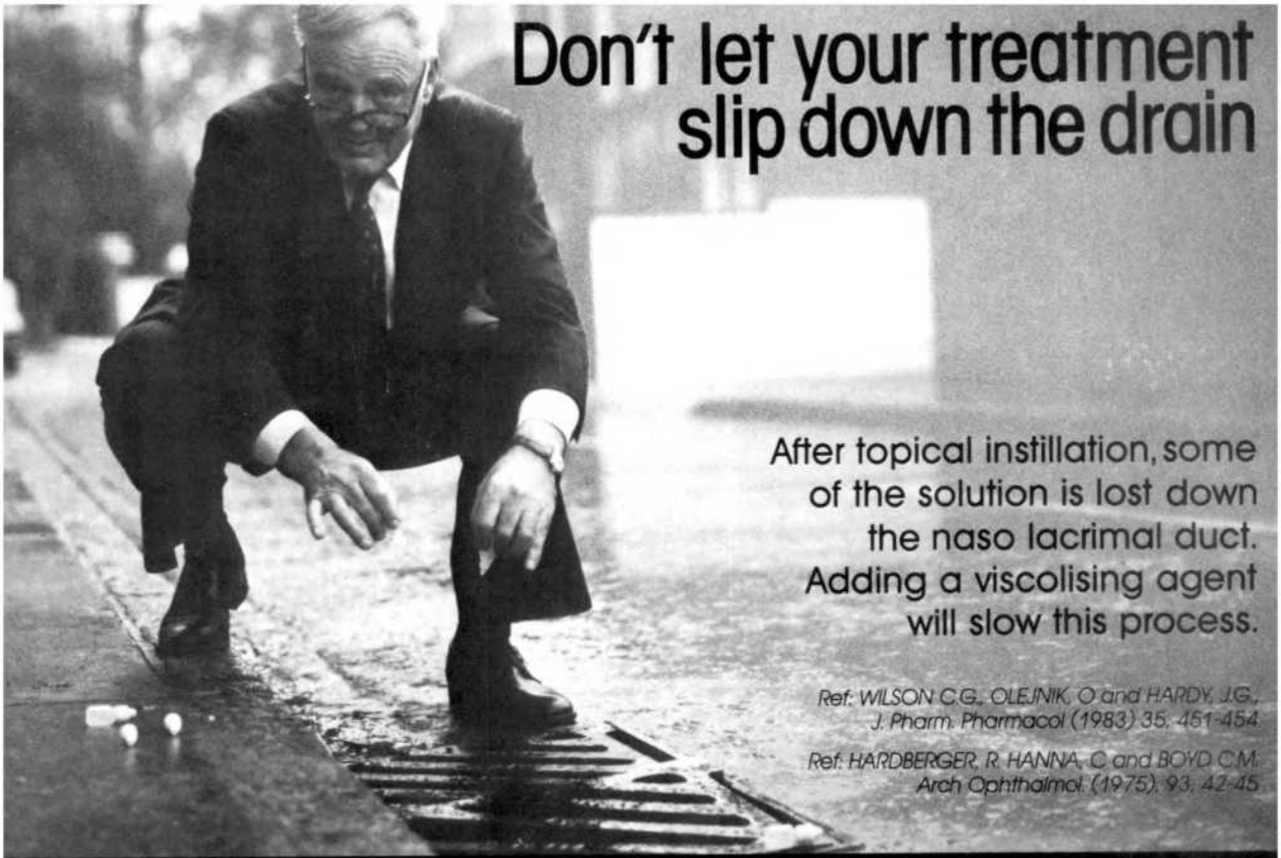
17 Smith RJH. Thrombotic glaucoma, a clinico-pathological study. *Acta Concilium Ophthalmologicum* 1954; **17:** 1164–75.

18 Muraoka K, Yokochi K. Origin of newly formed vessels from the optic disc. *Nippon Ganka Gakkai Zasshi* 1976; **80:** 1152–9.

19 McNaught EI, Foulds WS, Johnson NF. The permeability of the posterior blood ocular barrier after xenon photocoagulation: a study using labelled dextrans. *Br J Ophthalmol* 1981; **65:** 473–7.

20 Glaser BM, Campochiaro PA, Davis JL, Sato M. Retinal pigment epithelial cells release an inhibitor of neovascularization. *Arch Ophthalmol* 1985; **103:** 1870–5.

Accepted for publication 25 March 1987.



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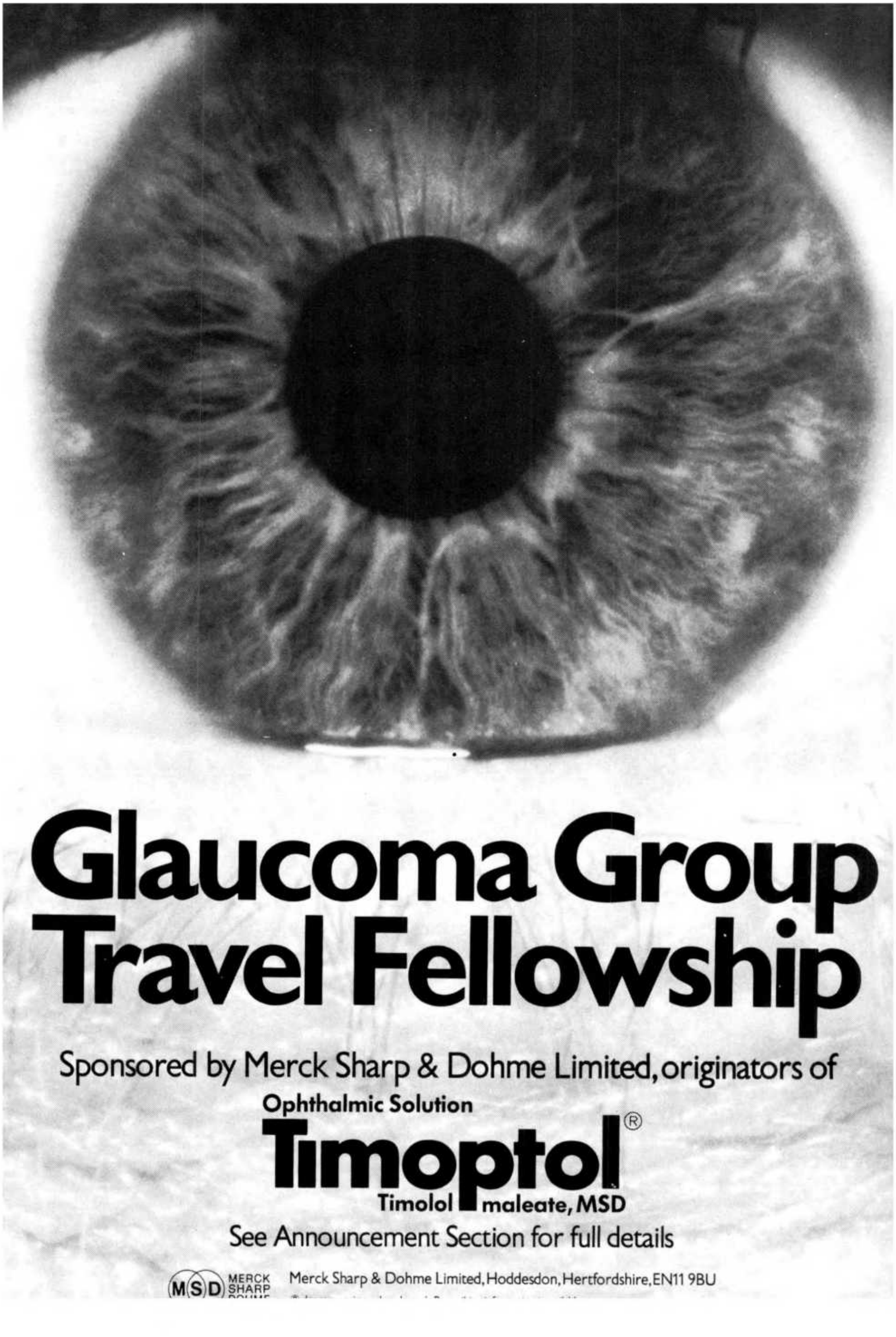

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Correspondence

Surgical corneal clouding

SIR, We were very interested to read the recent paper 'Morphological changes in the human corneal epithelium associated with surgical corneal clouding' by Hague, Dilly, and Thompson,[1] where they discuss the mechanisms of corneal clouding during cataract surgery which they attributed to epithelial changes.

We have recently looked at this problem of transient corneal clouding[2] and carried out a prospective study of 60 patients undergoing extracapsular cataract surgery. Our results suggest that the basic problem lies in the endothelium (as Hague *et al.* postulated), and we feel that any epithelial changes are likely to be secondary to this.

The corneal clouding we observed had the following features: it occurred rapidly after the start of the irrigation/aspiration phase of the surgery, often within seconds, and then resolved after 1-2 minutes when irrigation was stopped or when the anterior chamber contents were replaced by balanced salt solution or sodium hyaluronate (Healonid). High power examination of the cornea with the operating microscope in the presence of clouding revealed an optically clear epithelium but a degree of haziness at the level of the endothelium: in particular there appeared to be changes at the junctions between the endothelial cells.

We measured a series of parameters during surgery. These included the temperature of the infusion fluid, the duration of the infusion, the infusion flow rate, and the pH, osmolality, and chemical composition of the infusion fluids. Hartmann's solution was used as the infusion fluid during surgery on 40 eyes, and balanced salt solution (supplied by Alcon Laboratories (UK) Ltd) was used during surgery on 20 eyes. Our results revealed there was no association between the incidence of corneal clouding and the temperature of the infusion fluid, the duration of the infusion, or the flow rate of the infusion. However 90% of cases using balanced salt solution had no corneal haze compared with only 20% of cases using Hartmann's solution.

Further analysis of our results suggested that the large difference in osmolality between the two infusion fluids may be significant: the osmolality of aqueous is 300 mosmol/l, that of balanced salt solution 304 mosmol/l, and that of Hartmann's solution only 256 mosmol/1.

We postulated that the endothelial changes we observed may be due to a rapid change such as crystallisation or vacuolation occurring at the intercellular junctions. We concluded that the appearance of surgical corneal clouding was due to transient changes at the level of the endothelium, and these changes could be largely eliminated by using balanced salt solution as the infusion fluid.

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References

1 Hague S, Dilly N, Thompson GM. Morphological changes in the human corneal epithelium associated with surgical corneal clouding. *Br J Ophthalmol* 1987; **71**: 729–33.

2 McDonnell PJ, Spalton DJ. The maintenance of corneal clarity during extracapsular cataract surgery. *Eur J Implant Refract Surg* in press.

SIR, P J McDonnell and D J Spalton's work, reported in their letter shows that the importance of the endothelium in surgical corneal clarity has been identified by our two differing approaches. Dilly *et al.*[1] have shown that during osmotic insult to corneal endothelial cells there is considerable disruption of the junctions between the endothelial cells before there is any evidence of corneal stromal oedema. McDonnell and Spalton's results are in accord with these observations. Crystallisation we believe is a most unlikely event in the living intercellular space, especially in the presence of increased fluid flow between the cells. Dilly *et al.*'s observations are of increased vacuolisation between the cells. Similar changes have been shown between the epithelial cells of other compromised corneas, especially in neuroparalytic keratitis (Dilly and Mackie, unpublished observations).

Clouding is likely to be the result of a variety of factors; the time of onset and duration of clouding varies enormously between different patients. We would agree that there is a particular form of clouding which occurs almost immediately after the start of irrigation and clears quickly after infusion ceases. The speed of onset of this condition could certainly be explained by opacification at the level of the endothelium. We had attributed this change to a direct effect by pressure or mechanical forces of the infusion, but a change induced by chemical or osmolar insult seems equally feasible. We suggest that the endothelial changes are the first stage on the process leading to epithelial disruption.

In more prolonged clouding and clouding of later onset the epithelium certainly plays a part. The histological changes we identified are large enough to cause diffraction of light and hence result in opacity. Otherwise an explanation is also required for the clinical observation that removing the epithelium improves the view of intraocular structures. The use of balanced salt solution for infusion is a logical approach to this problem. McDonnell and Spalton's results seem encouraging. However, we have used balanced salt solution for infusion during surgery and still experienced problems with clouding of the cornea. We suspect that, although their suggestion may offer some improvement, it is not the complete answer to what is probably a heterogeneous problem.

We thank Drs McDonnell and Spalton for their interesting letter.

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Reference

1 Dilly PN, Cavanagh HD, Jester JV, Lemp MA. In vivo tandem scanning reflected light microscopy. II: Morphological demonstration of ouabain inhibition of rabbit corneal endothelial pump. *Invest Ophthalmol Vis Sci* 1987; **28**: (suppl, 3): 326.

Revision of ICRP report on reference man

SIR, In 1975 the International Commission on Radiological Protection (ICRP) published its publication 23, the *Report of the task group on reference man.* That report, with cited references ending in about 1970, is out of date and is currently being revised. The revision will include more emphasis on variations due to age, sex, and other individual differences in anatomical and physiological data and in gross and elemental composition of tissues. The emphasis in ICRP 23 is on data for radiation workers, and the new emphasis reflects the fact that radiation doses to the whole population are of increasing interest to ICRP and national bodies interested in radiation protection.

I have responsibility for updating the chapter of ICRP publication 23 relating to the eye. I would value comments from users of ICRP 23 who have found errors, omissions, or general shortcomings in the previous treatment of this topic. Any new published data which are considered relevant should be sent to me at the address below. The emphasis of concern in radiological protection relates to radiation induced visual impairment, primarily through cataract induction. While general contributions are encouraged, those relating to radiation effects are particularly welcomed. Ophthalmological data relating to the morphology of the anterior of the eye, the morphology of the iris, and its uptake of radioactive materials, to mention just three examples, are areas where recent contributions in journals such as this will prove useful in directing radiological protection guidelines.

M W CHARLES

Radiobiology Laboratory,
Berkeley Nuclear Laboratories,
Berkeley,
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GL13 9PB

Obituary

Surgeon Rear-Admiral D P Gurd, CB, DSc, MD, MCL, FRCS, FRACS

Surgeon Rear-Admiral Dudley Plunkett Gurd died on 9 August 1987 in an Italian hospital at the age of 77 as the result of a motor accident. He entered the Royal Navy as a surgeon lieutenant in 1934. In 1943 he was awarded the Gilbert Blane medal for services to naval medicine.

In 1952 he was seconded to St John Ophthalmic Hospital as warden, a post he held for three years during a most difficult time in the hospital's history when it was housed in three separate buildings in the old walled city of Jerusalem. His hard work in most trying conditions was rewarded by the Queen in the form of a knighthood of the Most Venerable Order of the Hospital of St John of Jerusalem. He served in naval hospitals in Malta, Barrow Gurney, Hong-Kong, Plymouth, and Haslar. He ended his naval career as surgeon rear-admiral and medical officer in charge of RN Hospital, Bighi, until 1966, when he took up private practice as an ophthalmologist.

Dudley kept in touch by letter with many colleagues with whom he had served during his long period as a naval officer. He had a great love of the Royal Naval Medical Service, as witness his many articles in the *Royal Naval Medical Gazette.* He was a dedicated ophthalmic surgeon and kept his knowledge upto date in this rapidly changing speciality. His years with the Order of St John in Jerusalem gave him confidence with the scalpel in the operating theatre, and he was ever grateful for the opportunity in mid-career to serve a demanding surgical apprenticeship and acquire the skills so necessary for competent practice in the most precise of all surgical disciplines. He was a happy and fulfilled individual and so was able to impart a warmth to his chatter with the young and the old with kindly words enriched by his soft and attractive Ulster accent.

He is survived by his wife Thérèsa Marie and his son and daughter, whose sadness is shared by his many admirers.

SJHM

Note

Research grants

The *David Cole Travel fellowship*, instituted by Merck Sharp and Dohme in memory of Professor David Cole, will assist a visit to a hospital or research centre during the academic year starting 1 October 1988. The award will be equivalent to £2000. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

The *Glaucoma Group Research grant*, sponsored by the International Glaucoma Association, will be available for a research project clinically orientated to glaucoma for 1988. The award will be equivalent to £2500. The grant may be used towards salary or project expenses or for buying equipment.

Both these awards are available to medical graduates and non-medical scientists resident in the United Kingdom or the Irish Republic. They may be held concurrently with other awards. Further details and application forms from Dr S Nagasubramanian, Secretary Glaucoma Group, Glaucoma Unit, Moorfields Eye Hospital, High Holborn, London WC1V 7AN. The closing date for applications is 15 June 1988. The successful candidate will be informed by August 1988.

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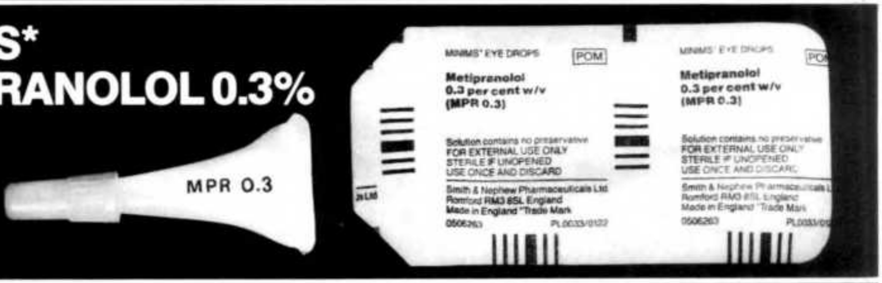

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If used as a diagnostic agent before planning a treatment programme then only one drop need be instilled.

In the treatment of post-operative rises in intra-ocular pressure the dosage and frequency should be at the discretion of the physician.

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The use of Minims metipranolol is not recommended in patients with obstructive airways disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Minims metipranolol should only be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block.

Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out.

Intra-ocular pressure should be determined at frequent and regular intervals.

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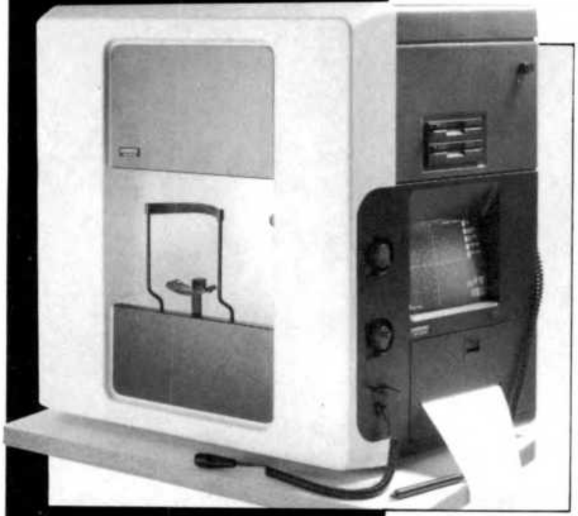

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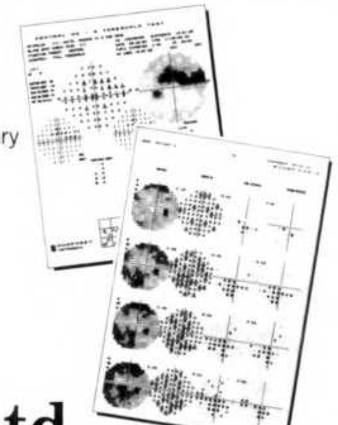

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Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

British Journal of Ophthalmology May 1988 Vol. 72 No. 5

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ASTM CODEN BJOPAL 72 (5) 321–400 (1988)

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British Medical Association Tavistock Square London WC1H 9JR

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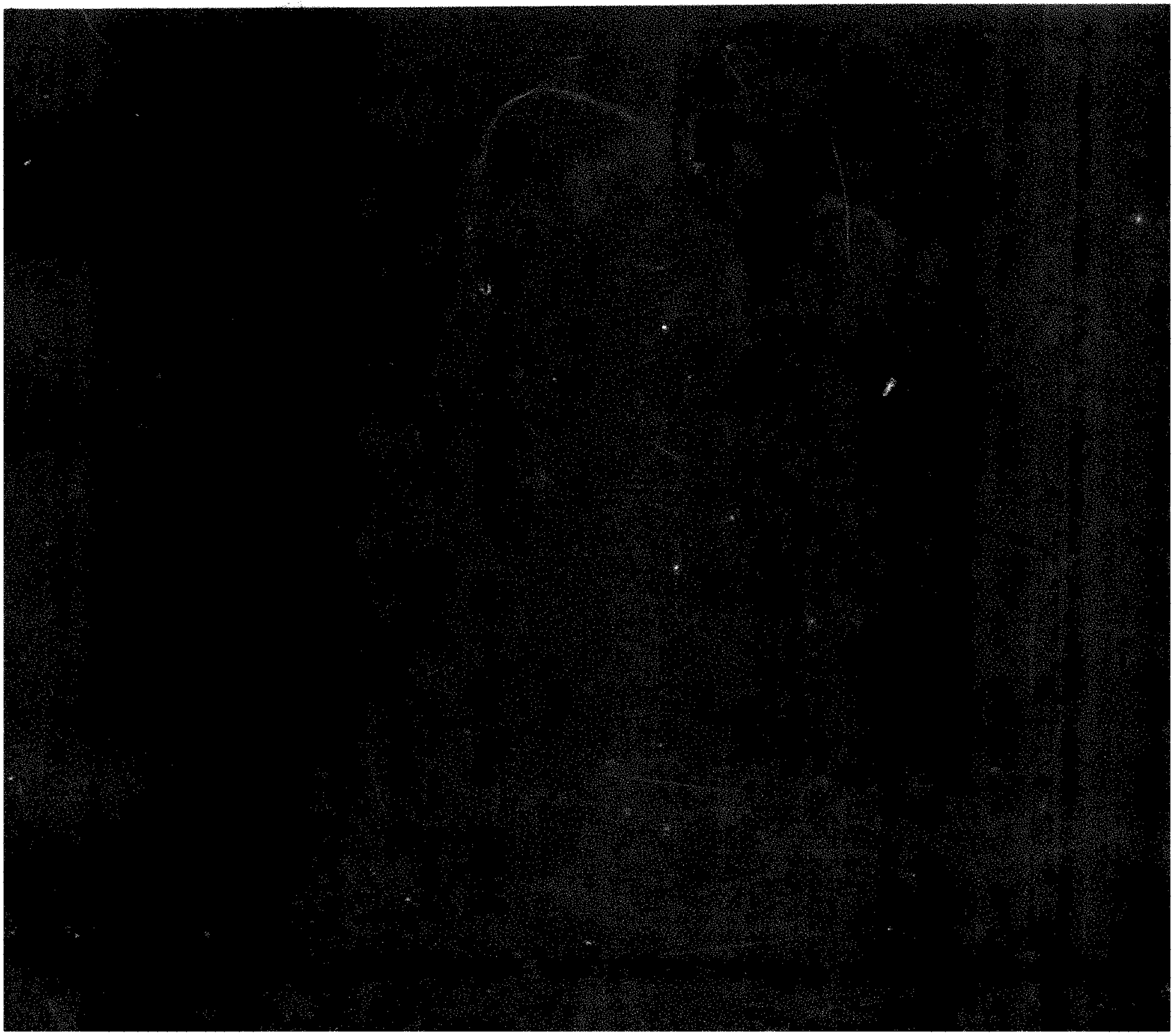

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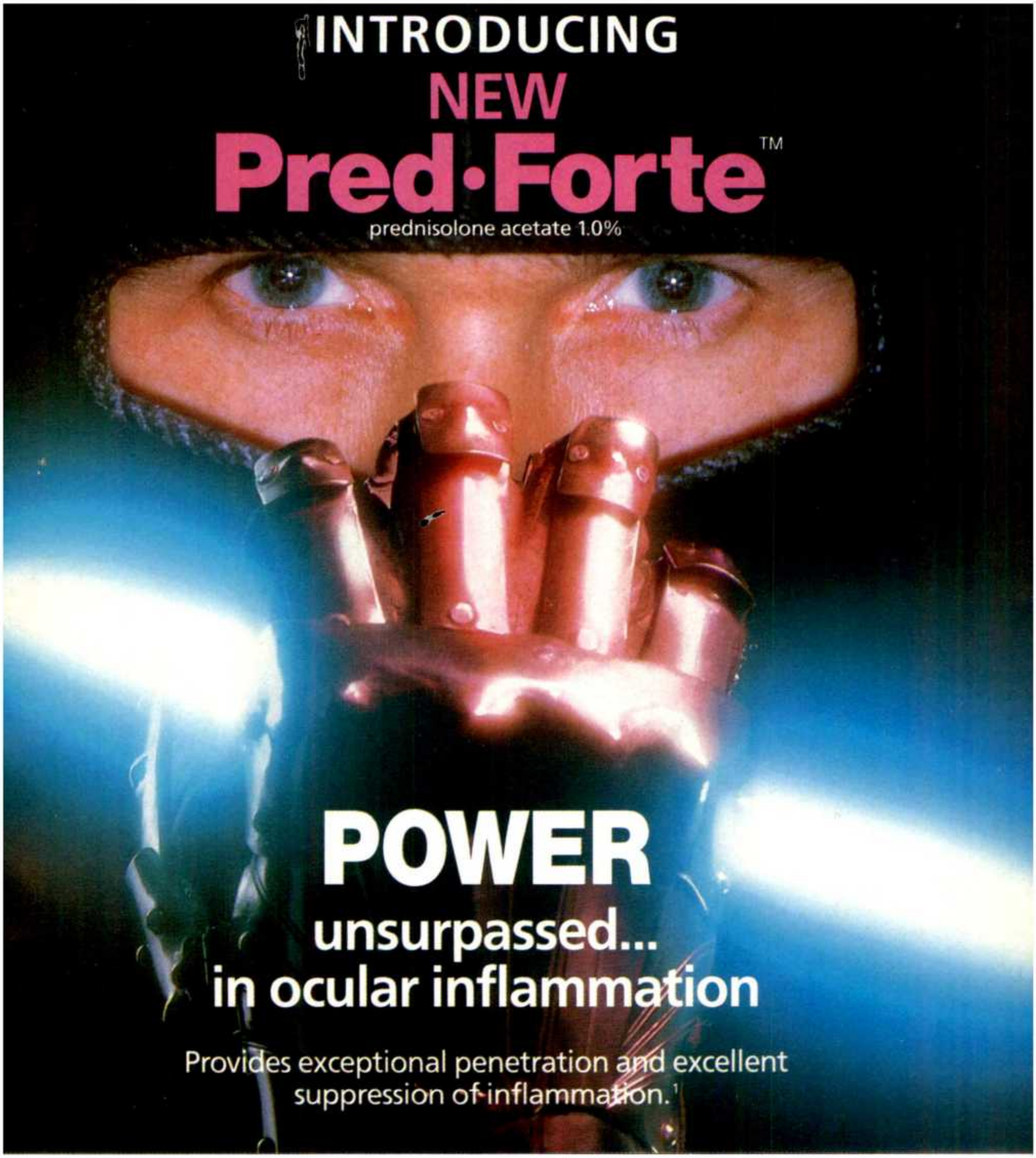
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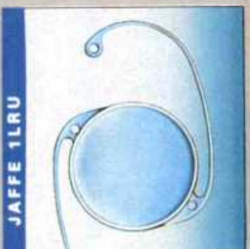

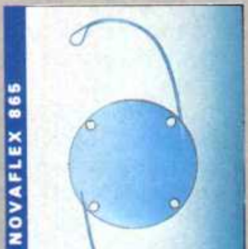

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British Journal of Ophthalmology, 1988, 72, 401–405

Panretinal cryotherapy in neovascular disease

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SUMMARY Panretinal cryotherapy (PRC) was used to treat 15 eyes with rubeosis, nine of which had established neovascular glaucoma, and seven eyes with proliferative diabetic retinopathy. The rubeosis regressed, with preservation of vision and return to normal of intraocular pressure, in all but one eye. With one exception all eyes with proliferative retinopathy also showed new vessel regression after treatment. PRC may be considered an effective alternative to retinal photocoagulation in the treatment of advanced rubeosis, early rubeotic glaucoma, and in certain circumstances proliferative diabetic retinopathy.

Iris and retinal neovascularisation occurring secondary to an ischaemic retinopathy may cause loss of vision by a number of mechanisms. These include vitreous haemorrhage, traction retinal detachment, and neovascular glaucoma.[1] For many years selective retinal ablation has been shown to induce regression of both retinal and iris neovascularisation in a significant number of cases.[2-4]

The first successful application of retinal ablation in the treatment of rubeotic glaucoma was in 1960, when 360° ablation of the retina anterior to the equator was performed with surface diathermy.[5] In 1964 cryotherapy was substituted, but when it was limited to the anterior retina many eyes lost light perception.[6] Panretinal cryotherapy (PRC) applied to the retina posterior to the equator has been advocated as a method of retinal ablation, but reports to date have concluded that PRC should be withheld until rubeotic glaucoma is present because of the risk of serious complications,[7] or the PRC has been combined with cyclocryotherapy.[8]

Our study presents the outcome of 22 eyes treated with PRC in the last six years at the Oxford Eye Hospital. The study includes nine eyes with neovascular glaucoma, six with advancing rubeosis, and seven with proliferative diabetic retinopathy.

Materials and methods

All eyes receiving PRC from one clinic between January 1979 and December 1985 were included in this study. This method of retinal ablation was adopted if poor media clarity, poor pupillary dilatation, extensive retinal oedema, or patient intolerance prevented adequate photocoagulation.

Prior to PRC 10 eyes had received laser or xenon panretinal photocoagulation which had not produced neovascular regression.

Where previous photocoagulation to the posterior retina was not considered to be sufficient, or no treatment had been given in the past, xenon photocoagulation was applied around the vessel arcades and temporal to the macula immediately before PRC, with the same retrobulbar anaesthetic. In five eyes PRC was used alone (eyes 5 and 6, Table 1 and eyes 1, 2, and 3 Table 2). One eye early in the series had cyclocryotherapy performed with the PRC (eye 1 Table 1).

PRC can be delivered under local or general anaesthesia. A 360° peritomy is performed, and 4/0 silk traction sutures are placed beneath the four rectus muscles to aid exposure. A total of 40 freeze-thaw applications with the 2·5 mm retinal cryoprobe are delivered under indirect ophthalmoscopic view where possible. Each quadrant receives 10 applications, a row of four centred on the equator followed by two circumferential rows of three posteriorly. Each application produces an area of retinal ablation of approximately 12 mm², and applications should be just confluent. No applications are performed within 5 mm of the macula or 3 mm of the disc. The time taken to produce the desired iceball is measured during initial application and varies from 5 to 10 seconds. It is important to measure the time for posterior applications, as these will be slightly longer than for anterior. This is due to the increased scleral

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and choroidal thickness encountered posteriorly and a greater tendency for heat to be absorbed from surrounding orbital tissue. If posterior applications are not delivered under direct vision, then a longer application time may be required to achieve the desired reaction.

When photocoagulation is to be given, it should be done before PRC, as there will be too much chemosis or corneal epithelial changes to allow effective light coagulation for some days. This is due to either difficulty in applying a contact lens or a reduction in the clarity of the cornea.

The area of retinal ablation produced by the above method of PRC has been determined with the following mathematical model:

If the area of retina posterior to the equator is assumed to be one half of a sphere with radius 12 mm, then the area of retina available for treatment= $\frac{1}{2}6\pi r^2=1357$ mm² (where r is the radius).

It is not desirable to treat within 5 mm of the macula or 3 mm of the disc. Therefore the effective area for treatment reduces to $1357-75-44$ mm²= 1238 mm².

If one cryo application produces 12 mm² of retinal ablation, 40 applications produce 480 mm². Therefore the percentage of available retina treated= $\frac{480}{1238}\times100=39\%$.

This percentage will increase to between 45 and 50% of the retina posterior to the equator if xenon applications are delivered immediately prior to PRC.

Results

RUBEOTIC GLAUCOMA

Of the nine eyes with rubeotic glaucoma five were secondary to diabetic retinopathy (one eye had coexisting disc new vessels); three were secondary to central retinal vein occlusion (CRVO), and one followed central retinal artery occlusion (eye 9). So far all eyes have remained pain free, all showed regression of iris neovascularisation, and all but one eye had an intraocular pressure within the accepted normal range on no medication. This was the only eye to lose all light perception in this group during the follow-up period, which ranged from four months to three years. The visual acuity improved in two eyes, remained unchanged in four, and deteriorated in three (Table 1).

Case 1. This 69-year-old patient with diabetes mellitus for 12 years which had been controlled on oral hypoglycaemic agents. In December 1982 he had 255 laser burns to the posterior pole of his left eye (eye 7, Table 1) for maculopathy. No signs of neovascular disease were present at that time, the intraocular pressure was normal, and the acuity was measured at 6/9. Ten weeks later at a routine follow-up visit the eye was noted to have early rubeosis round the pupil margin, new vessels crossing the drainage angle temporally through 180°, and an intraocular pressure of 38 mmHg. Despite mild epithelial oedema of the cornea, the acuity remained at 6/9. PRC, incorporating 400 xenon burns to the posterior retina, was performed, and two weeks later the rubeosis had regressed and intraocular pressure returned to normal. The visual acuity fell to 6/36 postoperatively owing to macula oedema. This slowly improved, returning to 6/9 seven months later. Three years later the eye retained 6/9 acuity and has required only minimal laser therapy to control an area of peripheral retinal neovascularisation.

Table 1 *Rubeotic glaucoma eyes*

Eye	*Age*	*Primary disease*	*Acuity prior to PRC*	*Acuity at end of follow-up*	*IOP controlled*	*Rubeosis regressed*	*Follow-up (months)*
1	65	Diabetes	1/60	HM	Yes	Yes	24
2	68	Diabetes	CF	CF	Yes	Yes	21
3	74	Diabetes	6/24	6/18	Yes	Yes	12
4	74	CRVO	HM	NPL	No	Yes	10
5	87	CRVO	CF	HM	Yes	Yes	4
6	62	Diabetes	CF	6/60	Yes	Yes	4
7	69	Diabetes	6/9	6/9	Yes	Yes	36
8	60	CRVO	HM	HM	Yes	Yes	30
9	60	CRAO	NPL	NPL	Yes	Yes	30

CRAO=central retinal artery occlusion. CRVO=central retinal vein occlusion. CF=counting fingers. HM=hand movements. NPL=no perception of light.

Table 2 *Rubeosis with normal IOP*

Eye	*Age*	*Primary disease*	*Acuity prior to PRC*	*Acuity at end of follow-up*	*Rubeosis regressed*	*Follow-up (months)*
1	77	CRVO	6/36	6/12	Yes	20
2	42	CRVO	CF	CF	Yes	6
3	62	Diabetes	6/60	6/60	Yes	4
4	70	Diabetes	6/60	CF	Yes	22
5	71	Diabetes	CF	CF	Yes	2
6	76	CRVO	HM	CF	Yes	24

ADVANCING RUBEOSIS

Six eyes were treated for advancing rubeosis, three secondary to diabetes and three following CRVO. All six eyes showed regression of the rubeosis and none progressed to rubeotic glaucoma in the follow-up period, which ranged from two months to two years in this subgroup. Visual acuity either remained static or improved in all but one eye, which developed increased lens opacities (Table 3).

Case 2. A 62-year-old, mentally subnormal insulin-dependent diabetic of four years' duration was first seen in May 1985. She was referred with corneal oedema from rubeotic glaucoma in her right eye (eye 6, Table 1) following intracapsular surgery performed 15 months earlier. This was successfully treated with PRC under general anaesthesia. The left eye (eye 3, Table 2) which had also received intracapsular surgery elsewhere, developed rapidly advancing rubeosis during August and September 1985. On 3 October PRC was performed on the left eye, again under general anaesthesia owing to the patient's mental state, and two weeks later the rubeosis had regressed completely.

Four months after the treatment of the left eye both eyes had normal intraocular pressures, and neither eye showed any evidence of rubeosis. The patient retained 6/60 acuity in each eye, the reduction being due to pre-existing diabetic maculopathy.

RETINAL NEOVASCULARISATION

Seven eyes were treated with PRC for disc or peripheral retinal neovascularisation. In 6 eyes this was secondary to diabetes and one eye had suffered a CRVO. Of the six diabetic eyes four were treated with PRC as vitreous haemorrhage prevented safe photocoagulation and two PRC treatments were performed because the patients could not tolerate photocoagulation. The eye with CRVO and disc new vessels had such extensive retinal oedema that adequate photocoagulation was not possible.

In the four eyes with vitreous haemorrhage, visual acuity improved by 3 lines or more in 2 eyes and by one line in one eye (Table 3). Only one eye (eye 7, Table 3) lost vision, progressing via rubeotic glaucoma to no perception of light.

Case 3. A 47-year-old type 1 diabetic of 27 years' duration presented in 1980 with disc new vessels in his right eye (eye 1, Table 3). Argon laser and xenon arc panretinal photocoagulation failed to induce new vessel regression, and in December 1981 PRC was performed on this eye, when vitreous haemorrhage precluded further photocoagulation. Xenon panretinal photocoagulation to the left eye (eye 2, Table 3), performed in December 1981, was followed by a vitreous haemorrhage. At this time both eyes had significant vitreous haemorrhage, with increasing neovascularisation. PRC was performed on the left eye in February 1982. The vitreous haemorrhages in both eyes subsequently cleared, but the right eye suffered a further bleed in 1983 before clearing slowly. The left eye remained clear and maintained an acuity of 6/12 four years later. New vessels regressed in both eyes following PRC, but an epiretinal membrane causing macular traction had reduced visual acuity in the right eye.

Table 3 *Eyes with proliferative retinopathy*

Eye	*Primary disease*	*Vitreous haemorrhage*	*Acuity prior to PRC*	*Acuity at end of follow-up period*	*Regression of new vessels*	*Follow up (months)*
1	Diabetes	Yes	6/36	6/24	Yes	48
2	Diabetes	Yes	6/60	6/18	Yes	36
3	CRVO	No	CF	CF	Yes	19
4	Diabetes	No	6/9	6/12	Yes	8
5	Diabetes	No	6/12	6/12	Yes	48
6	Diabetes	Yes	HM	6/12	Yes	24
7	Diabetes	Yes	CF	NPL	No	48

Discussion

The natural course of rubeotic glaucoma often results in a blind and painful eye.[6] Rubeosis has been stated to occur always at the pupil margin prior to its occurrence in the anterior chamber angle.[9] Although all cases of early rubeosis do not necessarily progress to rubeotic glaucoma,[10–12] progression may be rapid, particularly in CRVO.[13] To produce arrest or regression of an advancing rubeosis without inducing significant visual loss is clearly a desirable aim.

Regression of rubeosis was reported following extensive diathermy ablation of retina anterior to the equator in 1961,[5] and since Krill *et al.*[14] demonstrated regression of iris rubeosis following panretinal photocoagulation many studies have produced similar results.[13 15 16] It has been suggested that rubeosis may be prevented in susceptible eyes by prophylactic photocoagulation.[13 17]

Our results of applying PRC to eyes with advancing rubeosis suggest that PRC should not be forgotten as an alternative method of selective retinal ablation when adequate photocoagulation cannot be performed. It appears to be effective in inducing regression of the rubeotic vessels without decreasing visual acuity when the protocol described above is followed.

PRC does not feature in a major review article in 1981 on the treatment of established neovascular glaucoma.[18] Although reported complications of PRC include traction retinal detachment,[7 17] no evidence of retinal traction is present in eyes with rubeotic glaucoma we have treated so far. Cyclocryotherapy, advocated as a suitable treatment in the past,[19] resulted in a 6% enucleation rate, with 14% of eyes becoming phthisical and 58% losing light perception in one series.[20] Valve implants, even when preceded by photocoagulation, fail to control intraocular pressure in many cases, often after repeated surgical procedures.[21]

In contrast, in our series control of intraocular pressure was achieved with no additional medication in eight out of nine eyes with neovascular glaucoma. Of particular note are two eyes (eyes 3 and 7, Table

1), one whose acuity increased slightly from 6/24 to 6/18 and other whose acuity remained at 6/9 three years following PRC. Both had pressures over 35 mmHg before PRC, with angle neovascularisation which regressed following treatment. Intermittent peripheral anterior synechiae persisted in each eye, but intraocular pressures were maintained at 12 and 16 mmHg respectively. Treatment in five other cases preserved navigational vision, and this was particularly valuable in eye number 8, an only eye.

Although the mean follow-up of 19 months in eyes treated for rubeotic glaucoma is short in relation to the 4½-year mean follow-up of Smith,[6] our patients appear stable at present, with light perception lost in only one eye. Neovascularisation regressed in this eye, but the drainage angle was irreversibly occluded by fibrous tissue and the glaucoma persisted.

Early treatment during the initial stages of raised intraocular pressure was emphasised when diathermy was used in retinal ablation,[5] and we support the concept that the timing of treatment appears crucial in rubeotic glaucoma and there should be no delay if vision is to be preserved. This was well demonstrated in the first two case reports, where early treatment induced resolution of rubeotic glaucoma in eyes 6 and 7 in Table 1 and almost certainly prevented the onset of glaucoma in eye 3 in Table 2.

It has been suggested that PRC can speed the rate of clearance of vitreous haemorrhage secondary to proliferative diabetic retinopathy, and this treatment has been cited as an alternative to vitrectomy when no retinal traction exists.[22] Our small series (Table 3) shows similar results, but the eye (eye 7 in Table 3) which progressed to rubeotic glaucoma and traction retinal detachment gives cause for concern. This eye was treated before ultrasound was available at the Oxford Eye Hospital and may have had pre-existing traction. We consider PRC should be used in the management of proliferative diabetic retinopathy with longstanding vitreous haemorrhage only when traction has been excluded by adequate retinal visualisation or ultrasound examination.

PRC is a relatively straightforward procedure to perform under local or general anaesthesia and can be quickly mastered by a surgeon with retinal experience. Regression of rubeotic vessels usually begins after a few days with complete resolution occurring after four to five weeks. Choroidal effusions are common, as is postoperative shallowing of the anterior chamber, though we have not experienced secondary angle closure to date. The intraocular pressure may also rise postoperatively, particularly in established glaucoma, and should be controlled by medical means. A transient reduction in acuity secondary to macular oedema in eyes with good vision may also occur as in case report 1, and patients should be informed that this may happen.

We believe PRC to be most effective when used in conjunction with photocoagulation at the posterior pole but have demonstrated that PRC will produce neovascular regression in certain eyes when used alone.

We recommend the use of PRC in the management of early rubeotic glaucoma, when advancing rubeosis threatens a normotensive eye, and suggest that PRC should be considered in selected cases of proliferative diabetic retinopathy where photocoagulation cannot be delivered adequately owing to media opacities.

References

1 Newell FW. *Ophthalmology: principles and concepts*. 5th ed. St Louis: Mosby, 1982: 441–3.

2 Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. The second report of diabetic retinopathy study findings. *Ophthalmology* 1978; **85**: 82–106.

3 Little ML, Rosenthal AR, Dellaporta A, Jacobson DR. The effect of panretinal photocoagulation on rubeosis iridis. *Am J Ophthalmol* 1976; **81**: 804–9.

4 Murphy RP, Egbert PR. Regression of iris neovascularization following panretinal photocoagulation. *Arch Ophthalmol* 1979; **79**: 700–2.

5 Smith RJH. Neovascularisation in ocular disease. *Trans Ophthalmol Soc UK* 1961; **81**: 125–44.

6 Smith RJH. Rubeotic glaucoma. *Br J Ophthalmol* 1981; **65**: 606–9.

7 Mohan V, Eagling EM. Peripheral retinal cryotherapy as a treatment for neovascular glaucoma. *Trans Ophthalmol Soc UK* 1978; **98**: 93–5.

8 May DR, Bergstrom TJ, Parmet AJ, Schwartz JG. Treatment of neovascular glaucoma with trans scleral pen-retinal cryotherapy. *Ophthalmology* 1980; **87**: 1106–11.

9 Wand M, Dueker DK, Aiello LM, Grant WM. Effects of panretinal photocoagulation on rubeosis iridis, angle neovascularization and rubeotic glaucoma. *Am J Ophthalmol* 1978; **86**: 332–9.

10 Madsen PH. Rubeosis of the iris and haemorrhagic glaucoma in patients with proliferative diabetic retinopathy. *Br J Ophthalmol* 1971; **55**: 368–71.

11 Olrt V. The frequency of rubeosis iridis in diabetic patients. *Acta Ophthalmol (Kbh)* 1971; **49**: 301–7.

12 Madsen PH. Haemorrhagic glaucoma: comparative study in diabetic and non-diabetic patients. *Br J Ophthalmol* 1971; **55**: 444–50.

13 May DR, Klein ML, Peyman GA, Raichand M. Xenon arc panretinal photocoagulation for central retinal vein occlusion: a randomised prospective study. *Br J Ophthalmol* 1979; **63**: 725–34.

14 Krill AE, Archer D, Newell FW. Photocoagulation in complications secondary to branch vein occlusion. *Arch Ophthalmol* 1971; **85**: 48–60.

15 Laatikainen L, Kohner EM, Khoury D, Blach RK. Retinal photocoagulation in central retinal vein occlusion: a randomised controlled clinical trial. *Br J Ophthalmol* 1977; **61**: 741–3.

16 Blach RK, Hitchings RA, Laatikainen L. Thrombotic glaucoma prophylaxis and management. *Trans Ophthalmol Soc UK* 1977; **97**: 275–9.

17 Flanagan DW, Blach RK. Place of panretinal photocoagulation and trabeculectomy in the management of neovascular glaucoma. *Br J Ophthalmol* 1983; **67**: 526–8.

18 Weber PA. Neovascular glaucoma. Current management. *Surv Ophthalmol* 1981; **26:** 149–53.

19 Fiebel RM, Bigger JF. Rubeosis iridis and neovascular glaucoma. Evaluation of cyclocryotherapy. *Am J Ophthalmol* 1972; **74:** 862–7.

20 Krupin T, Mitchell KB, Becker B. Cyclocryotherapy in neovascular glaucoma. *Am J Ophthalmol* 1978; **86:** 24–6.

21 Krupin T, Kaufman P, Mandell A, Terry S, *et al.* Long term results of valve implants in filtering surgery for eyes with neovascular glaucoma. *Am J Ophthalmol* 1983; **95:** 775–82.

22 Mosler MA, Del Piero E, Gheewala SM. Anterior retinal cryotherapy in diabetic vitreous haemorrhage. *Am J Ophthalmol* 1985; **100:** 440–4.

Accepted for publication 25 March 1987.

British Journal of Ophthalmology, 1988, 72, 406–408

The Human Anterior Lens Capsule—an attempted chemical debridement of epithelial cells by ethylenediaminetetracetic acid (EDTA) and trypsin

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SUMMARY The addition of edetic acid (EDTA) or trypsin to the infusion during a simulated extracapsular cataract extraction on cadaver eyes facilitates the removal of lens epithelial cells from the anterior capsule. Modification of the chemical composition of infusions used during extracapsular surgery may maximise lens epithelial cell removal and hence reduce the incidence of opacification of the posterior capsule after cataract extraction.

A major cause of a poor visual outcome following extracapsular cataract extraction, with or without intraocular lens implantation, is opacification of the posterior capsule. Quoted incidences vary from 15% to 35% at two years[1] and 50% at three years,[2-4] and it is more frequent in children.[5-7] The average time to opacification is 26 months, with a range of three months to four years.[8]

It has been suggested that the chief cause of opacification following extracapsular surgery is proliferation of residual lens epithelial cells.[9] We have previously demonstrated that these cells are not removed during surgery but remain adherent to the anterior and equatorial capsule.[10] If these cells could be completely removed during surgery, the incidence and degree of posterior capsule opacification, and the subsequent need for secondary capsulotomy procedures, would be significantly reduced.

The purpose of this study was to assess the effectiveness of chemical substances in facilitating a complete removal of the lens epithelial cells from the anterior and equatorial capsule during an extracapsular cataract extraction. Two substances were selected. Edetic acid (EDTA) is a calcium chelating agent which is used to dissociate epithelial cells from basement membranes in in-vitro studies.[11] Trypsin is a proteolytic enzyme that specifically hydrolyses the acyl groups of lysine and arginine, important in intercellular bonding, and is again used to prepare isolated epithelial lens cell suspensions.[12]

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Materials and methods

Extracapsular cataract extractions were performed under standard microscopic operating conditions on fresh (≥48 h post mortem) human cadaver eyes. A full thickness section of cornea was removed at the start of the procedure to act as a histological control in each case. Extracapsular extraction then proceeded with an anterior capsulotomy, nucleus expression, and as complete a removal of soft lens matter as possible by means of coaxial irrigation-aspiration cannula.

Six pairs of eyes were operated upon, the only variable being the composition of the irrigation fluid. This consisted of:

Normal balanced saline solution	2 eyes
30 mM EDTA solution	2 eyes
15 mM EDTA solution	2 eyes
5 mM EDTA solution	2 eyes
2% Trypsin solution (Sigma, Poole, UK)	2 eyes
0·5% Trypsin+5 mM EDTA solution	2 eyes.

The eyes and the control cornea were then fixed, sectioned, and stained as previously described.[10]

Results

Histological examination of the sections revealed that the epithelial cells of the lens remained attached to the anterior capsule when the infusion contained balanced saline only (Fig. 1). The cells have a normal morphological appearance and intercellular junctions are similarly undisturbed.

Sections from eyes that were infused with 15 mM

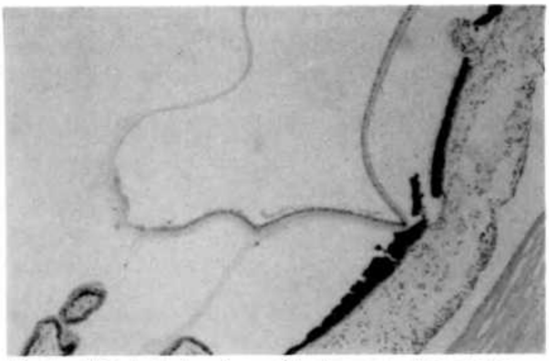

Fig. 1 *Histological sections of the lens capsule in an eye irrigated with balanced saline only. The lens epithelial cells remain adherent to the capsule and their morphology is undisturbed. Haematoxylin and eosin stain. Field width 2·8 mm.*

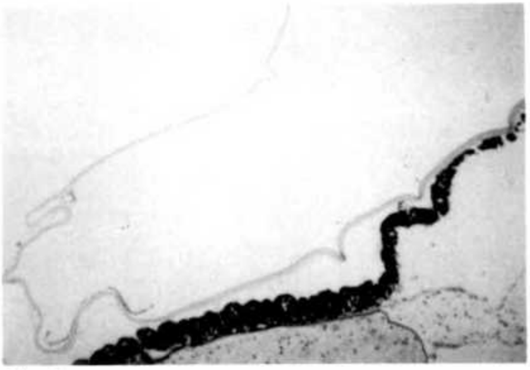

Fig. 2A

Fig. 2 *Histological sections of the lens capsule in an eye irrigated with (A) 15 mM EDTA (field width 2·8 mm) and (B) 30 mM EDTA (field width 1·1 mm). The epithelial cells have separated from the lens capsule as a sheet. The lens zonules in these specimens (not shown in fig. 1) were intact.*

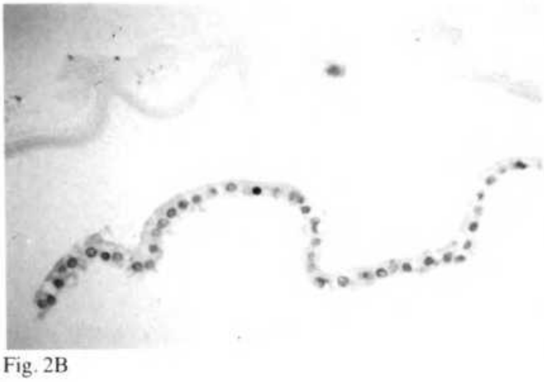

Fig. 2B

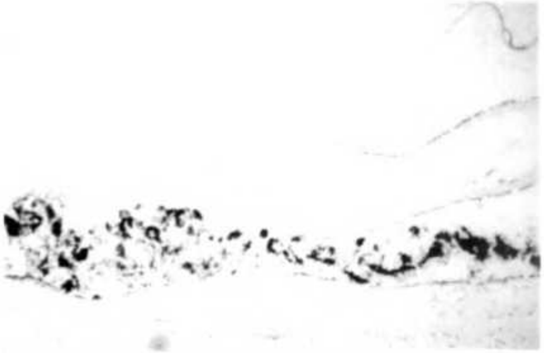

Fig. 3 *Histological section of the lens capsule in an eye irrigated with 2% trypsin. The epithelial cells are partially stripped from the capsule but their morphology is altered and intercellular junctions are disrupted. There is much pigment deposition—presumably derived from the iris. Field width 1·1 mm.*

and 30 mM EDTA (Figs. 2A, B) showed that the anterior epithelial cells had fallen away from the capsule as a sheet, while the intercellular junctions remained relatively intact. The zonule of the lens appeared relatively undamaged. While both infusions of 15 mM and 30 mM EDTA caused deepithelialisation of the capsule, 5 mM EDTA did not disturb the cell capsule attachments.

Sections from eyes infused with 2% trypsin showed that the epithelial cells had been stripped only in places from the capsule (Fig. 3), and there were marked morphological changes in the epithelial cells. The cytoplasm was swollen, cell borders were irregular, and intercellular junctions were broken, resulting in cells becoming separated from each other. There was extensive pigment deposition at the capsule, suggesting proteolytic damage to the iris. The zonules appeared fragmented, also indicating some damage.

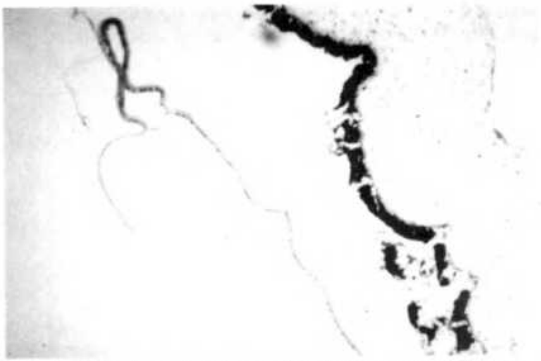

Fig. 4 *Histological sections of the lens capsule in an eye irrigated with 5 mM EDTA and 0·5% trypsin. The epithelial cells remain adherent to the lens capsule. Field width 1·1 mm.*

Those eyes infused with 5 mM EDTA and 0·5% trypsin did not show epithelial cell stripping (Fig. 4). However, there was pigment deposition indicating some iris damage.

The corneas in all these eyes were also examined histologically, and there was no evidence of stripping or damage to the endothelial cells.

Discussion

Irrigation and aspiration alone are incapable of dislodging lens epithelial cells from the anterior lens capsule. The capsule is secreted by the epithelial cells as their basement membrane and differs both chemically and ultrastructurally from the lens zonule[13] to which it is attached.

The lens epithelial cells lie under the anterior and equatorial capsule, with their smooth bases apposed to the capsule and their apices facing the interior of the lens. Adjacent cells are attached to each other by a small zonula occludens at the apical borders and occasionally by a macula adherens. No cement substance or other extracellular material is seen between the base of the epithelium and the capsule or between the apices of the epithelium and the first layer of lens cells.[13]

EDTA in high enough concentrations is effective in disrupting the cell capsule bond and results in the cells falling away as a sheet. The intercellular junctions are not affected. Trypsin is effective in disrupting both cell capsule and intercell bonds but appears to inflict more damage on associated structures such as the iris in vitro—as would be expected from a proteolytic enzyme involved in digestion.

That the lens epithelial cells are the major contributor to opacification of the posterior capsule has been demonstrated by pathological[9 14–16] in-vitro cell culture[10] and animal[17] studies. Any procedures that may maximise their surgical removal may be of great clinical benefit. EDTA is possibly a better chemical debrider on theoretical grounds, since in the short term its action is extracellular, it is not an enzyme, and its effects are reversible by the addition of calcium to the environment. Our histological studies show that EDTA exerts less damage to surrounding structures than does trypsin.

Although there was no obvious damage to the corneal endothelium, it is impossible to estimate any potential side effects that may be incurred in a living eye from this post-mortem study. Further animal studies will be necessary before the safety and efficacy of EDTA as a routine constituent of intraocular irrigation fluids in humans can be fully assessed.

References

1 Jaffe NS. Results of intraocular lens implant surgery. *Am J Ophthalmol* 1978; **85:** 13–23.
2 François J. Late results of congenital cataract surgery. *Ophthalmology* 1979; **86:** 1586–97.
3 Kraff MC, Sanders DR, Lieberman HL. Total cataract extraction through a 3 mm incision. A report of 650 cases. *Ophthalmic Surg* 1979; **10:** 46–54.
4 Wilhemus KR, Emery JM. Posterior capsule opacification following phocoemulsification. In: Emery JM, Jacobson AC, eds. *Current concepts in cataract surgery: selected proceedings of the sixth biennial cataract surgical congress.* St Louis: Mosby, 1980: 304–8.
5 Hiles DA, Watson BA. Complications of implant surgery in children. *J Am Intraocul Implant Soc* 1979; **5:** 24–32.
6 Binkhorst CD, Gobin MM. Injury to the eye with lens opacity in young children. *Ophthalmologica* 1964; **148:** 109–83.
7 Binkhorst CD. The iridocapsular (two loop) lens and iris clip (four loop) lens in pseudohphakia. *Ophthalmology* 1973; **77:** 589–617.
8 Wilhemus KR, Emery JM. Posterior capsule opacification following phacoemulsification. *Ophthalmic Surg* 1980; **11:** 264–7.
9 Green WR, McDonnell PJ. Opacification of the posterior capsule. *Trans Ophthalmol Soc UK* 1985; **104:** 727–39.
10 Jacob TJC, Humphry RC, Davies EG, Thompson GM. Cytological factors relating to posterior capsule opacification following cataract surgery. *Br J Ophthalmol* 1987; **71:** 659–63.
11 Gospodarowicz D, Massoglia S. Plasma factors involved in the in vitro control of proliferation of bovine lens cells in defined medium. Effect of fibroblast growth factor on cell longevity. *Exp Eye Res* 1982; **35:** 259–70.
12 Hamada Y, Okada TS. The differentiating ability of rat lens epithelial cells in culture. *Dev Growth Diff* 1977; **19:** 265–73.
13 Hogan MJ, Alvarado JA, Weddell JE. *Histology of the human eye. An atlas and textbook.* Philadelphia: Saunders, 1971: Ch. 12.
14 McDonnell PJ, Zorzin MA, Green WR. Posterior capsule opacification in pseudophakic eyes. *Ophthalmology* 1983; **90:** 1548–53.
15 McDonnell PJ, Stark WJ, Green WR. Posterior capsule opacification: a specular microscope study. *Ophthalmology* 1984; **91:** 853–6.
16 Hiles DA, Johnson BC. The role of the crystalline lens epithelium in postpseudophakos membrane formation. *J Am Intraocul Implant Soc* 1980; **6:** 141–7.
17 Odrich MG, Hall SJ, Worgul BV, Trokel SL, Rini FJ. Posterior capsule opacification: Experimental analysis. *Ophthalmic Res* 1985; **17:** 75–84.

Accepted for publication 2 April 1987.

British Journal of Ophthalmology, 1988, **72,** 409–412

Bullous keratopathy: a study of endothelial cell morphology in patients undergoing cataract surgery

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SUMMARY Preoperative and postoperative endothelial cell morphology was examined in three types of patients participating in a randomised, controlled trial of cataract surgery. The first sustained modest endothelial cell loss and served as controls, the second and third sustained high cell loss, but only the latter progressed to bullous keratopathy. The technique of examining endothelial cell morphology is described and its validity assessed. Measures of cell area, number of sides, side length, and variation in cell size and cell shape were utilised. No significant differences were found between the three groups by any of the preoperative morphological measures. Furthermore, postoperative values of variation in cell shape and cell size did not differ significantly between the groups. No evidence was found in our patients to support the hypothesis that eyes at particular risk of developing bullous keratopathy may be differentiated on the basis of their preoperative or early postoperative endothelial cell morphology.

Bullous keratopathy has become the commonest condition requiring penetrating keratoplasty.[1 2] The increase in incidence of bullous keratopathy may have resulted from the increased volume of cataract surgery, new surgical techniques, or increased implantation of intraocular lenses of varying design. The exact contribution of each potential cause has not been determined, but a better understanding is desirable to identify vulnerable cases and risk factors. Much emphasis has been placed recently on the morphology of the corneal endothelium,[3] and a suggestion has been made that eyes developing bullous keratopathy may have more preoperative polymorphism or pleomorphism. The purpose of this paper is to report on an examination of endothelial cell morphology pre- and postoperatively of eyes developing bullous keratopathy and compare that to findings in controls.

Material and methods

Patients studied were participating in a randomised controlled trial of cataract surgery which has been in progress for six years, for five of which there was no loss to follow-up except through death. Detailed accounts of the trial design and surgical techniques have already been reported.[4] The majority of patients were treated by one experienced surgeon who contributed 274 eyes of 268 patients with a mean age of 72 years and a range of 55–89 years. All the patients in the present study on bullous keratopathy contributed only one eye in the study and had only one eye operated on at the time of this assessment. Patients were randomised into one of three treatment groups which were:

Group A. Intracapsular extraction followed by contact lens fitting.

Group B. Intracapsular extraction and implantation of an iris supported lens—Federov I.

Group C. Extracapsular extraction and implantation of a Binkhorst two-loop iridocapsular lens.

Patients had endothelial cell photographs taken preoperatively, at one month, six months, and yearly after surgery. Cell densities were derived in all patients by a counting method which masks the patients' identity. The method of photography[5] and precision estimates[6] have been reported.

A detailed protocol and structured follow-up enabled us to identify three groups of patients. The first group were patients who underwent uneventful surgery and postoperative recovery and who sustained only modest endothelial cell loss (mean cell loss six months after operation=10·03%, SD=6·56%). This group served as controls. The second group were patients whose surgery and/or

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postoperative recovery was complicated and who sustained large cell loss in the early postoperative period but did not develop bullous keratopathy (mean cell loss six months after operation=33·66%, SD=18·2%). The third group sustained large endothelial cell loss and developed bullous keratopathy (mean cell loss six months after operation=31·68%, SD=16·9%).

Preoperative and one month postoperative endothelial cell photographs from these three groups of patients were enlarged to allow analysis of cell morphology. The original magnification factor of 148 times was increased to 311 times and photographic contrast enhancement techniques were used in developing the film. The apices of the endothelial cells were then digitised on a Summagraphics MM 1201 digitising pad with a digitising pen and the data analysed by an IBM personal computer. Digitisation in this context means the characterisation of points by a set of numbers. The digitising tablet employed was able to determine the location of points ±0·625 mm with repeatability for the same point of ±0·25 mm or better (manufacturers' specification). For most photographs 75 cells were digitised and in others a minimum of 50 cells. Evidence for the adequacy of a 50-cell sample has been presented by Bourne.[7]

A program was developed which, from digitisation of the apices of endothelial cells, will compute the area of individual cells, that of the smallest and largest cells, a range of cell areas, side lengths and the number of sides, and the perimeter of each cell. From these basic data two further measures were computed. As an index of variation in cell area the coefficient of variation was calculated by dividing the standard deviation of the cell area by the mean cell area and then expressing this as a percentage. This ratio is independent of cell size and provides a quantitative measurement of variation in cell area (polymegathism). Variation in cell shape was quantified by comparing the digitised cells with equilateral hexagons. For an equilateral hexagon the ratio of area:perimeter^2 is a constant (sin 60°/12 or 0·07217). The deviation of digitised cells from hexagonality may be expressed as a percentage according to the equation $[(A/p^2)/0{\cdot}07217]\times 100$, such that, if the cell is an equilateral hexagon, the index will be 100. This value is a dimensionless expression of variation in cell shape (pleomorphism) which is independent of size and orientation.[8]

VALIDATION OF DIGITISATION TECHNIQUE

To test the accuracy of the computerised digitisation, 50 hexagons of calculated area (confirmed by weighing) were digitised five times.

To estimate precision, 50 endothelial cells from two specular microscopic photographs were digitised five times, one with a population of large cells and the other small cells. Thus five mean cell areas were obtained for each photograph.

Table 1 *Validation study*

Digitisation procedure	*Mean cell area of*	
	Large cells	*Small cells*
50 Cells from 2 photos five times	287·85±2·9 SD=1·0% of mean	134·10±1·8 SD=1·3% of mean
3 Central photos of 2 patients	292·93±3·4 SD=1·2% of mean	119·33±1·9 SD=1·6% of mean

Reproducibility was examined by digitising three specular microphotographs of the central corneal endothelium from two patients, again one with large and the other with small endothelial cells.

Results

The validation study showed a high degree of accuracy, precision, and reproducibility. Accuracy: the mean value of digitising 50 hexagons of calculated area five times differed from the calculated area by only 3·15%. Precision: repeated digitisation of 50 cells from a sample of large and a sample of small cells produced a standard deviation of 1·0 and 1·3% of the mean (Table 1). As expected, the value was smaller for large cells. The mean cell area could be measured with a precision of 1·15% by this technique. Reproducibility: the variation of mean cell area between the three photographs of the same patient was about 1·2–1·6% (Table 1).

The results of the morphological analysis of preoperative photographs from the three groups of eyes are shown in Table 2. There was no significant difference in the values of the different features except for mean cell area. The mean area of the smallest cells in eyes developing bullous keratopathy was significantly larger, probably through inclusion of two eyes with low cell density.

One month postoperatively, as expected, the values of all the features examined were significantly greater in the two groups, with high cell loss in comparison with the control group. However, neither coefficient of variation nor deviation from hexagonality showed any significant change. In a few patients the photographs were not of good enough quality for digitisation.

Discussion

The validation study showed a high degree of accuracy, precision, and reproducibility. Our results on precision and reproducibility compare very favourably with those reported by others.[7,9–11]

Table 2 *Morphological analysis of preoperative photographs*

	Controls n=15	*High cell loss, patients n=7*	*Bullous keratopathy, patients n=9*
Mean cell area	427·66 SD=75·56	430·94 SD=53·66	494·75† SD=104·39
Mean cell density	2802 SD=356	2534 SD=410	2483 SD=490
Mean area of smallest cell	180·71 SD=33·87	170·81 SD=23·59	233·82* SD=61·51
Mean area of largest cell	855·08 SD=176·88	865·76 SD=212·10	933·59 SD=221·94
Mean no. of sides per cell	6·01 SD=0·14	5·87 SD=0·10	6·00 SD=0·09
Mean side length	13·07 SD=1·05	13·53 SD=0·96	14·16 SD=1·42
Coefficient of variation	31·09 SD=6·71	30·41 SD=5·95	28·58 SD=4·13
Deviation from hexagonality	92·98 SD=1·43	92·26 SD=0·90	93·51 SD=1·21
Cell density ranges	1333	1186	1260

Areas in μm^2; density in cells/mm^2; length in μm.
*p=0·05 vs controls. †No significant difference from controls.

Preoperative assessment of endothelial cell morphology showed values for mean cell area consistent with typical endothelial cell densities for this age group of patients (for example, for controls= 2338 cells/mm^2).[12] Hexagons were the most commonly observed cell shape as shown by the mean number of sides—close to six observed in each group (Fig. 1). The values for the coefficient of variation were within the range previously quoted for patients obtained before cataract surgery[3] and suggest that cells were relatively uniform in size. Similarly values for deviation from hexagonality were all very high, suggesting homogeneity of cell shape.

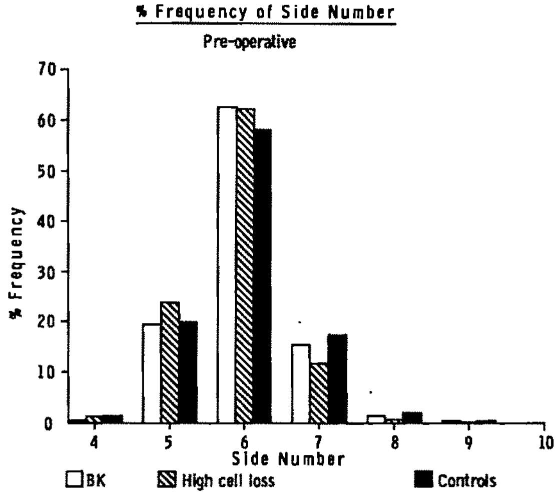

Fig. 1 *Frequency distribution of the number of sides of the cells in the three groups of eyes before operation.*

Interestingly there was no significant difference between the three groups on any of the preoperative morphological measures studied except mean area of the smallest cell area between controls and bullous keratopathy (BK) patients. This is due to the fact that two of the eyes with BK had a preoperative density of <2000 cells/mm^2. It has been suggested that cellular polymegathism and pleomorphism reflect susceptibility to surgical trauma[13 14] and in particular postoperative corneal oedema.[3] However, our results suggest that for eyes without pre-existing disease preoperative endothelial morphology does not differentiate either patients who will undergo large endothelial cell losses or those who will progress to bullous keratopathy from controls.

Postoperative analysis of endothelial cell morphology revealed expected increases in mean cell area as well as area of the smallest and the largest cells in all groups, with the appearance of cells with the greater number of sides in the high cell loss groups (Table 3 and Fig. 2). However, while cells increased in size, the fairly constant values for coefficient of variation and deviation from hexagonality suggest that in general they increased uniformly, so that variation in size and shape between cells changed little. It is just possible that at one month after surgery central cellular rearrange-

Table 3 *Morphological analysis of postoperative photographs*

	Controls n=12	*High cell loss, patients n=6*	*Bullous keratopathy, patients n=5*
Mean cell area	498·20 SD=64·03	923·03*** SD=232·46	885·83*** SD=56·52
Mean cell density	2436 SD=269	1294 SD=212	1602 SD=69
Mean area of smallest cell	244·06 SD=65·35	383·26* SD=141·58	432·34*** SD=90·08
Mean area of largest cell	926·46 SD=120·01	1792·09*** SD=510·34	1529·30*** SD=186·03
Mean no. of sides per cell	5·97 SD=0·10	6·21* SD=0·22	6·07* SD=0·05
Mean side length	14·31 SD=0·86	18·61*** SD=2·56	18·86*** SD=0·49
Coefficient of variation	28·55 SD=3·58	31·39† SD=5·01	26·28† SD=1·95
Deviation from hexagonality	92·37 SD=1·21	92.55† SD=1·47	92·19† SD=2·51
Cell density ranges	707	551	133

Areas in μm^2; density in cells/mm^2; length in μm.
***p<0·001
** p<0·01 } vs controls. †No significant difference from controls.
* p<0·05

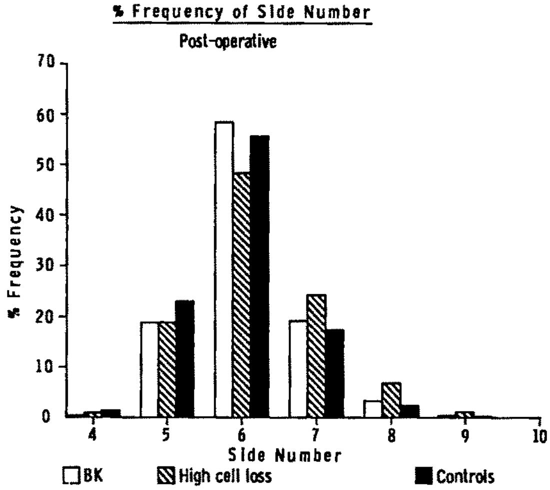

Fig. 2 *Frequency distribution of the number of sides of the cells from the same eyes as in Fig. 1 one month after operation.*

ment to compensate for cell loss may not have been completed, but this should not happen to the same degree in all three groups. It is of interest that patients who later developed corneal decompensation did not show significantly greater polymegathism or cellular pleomorphism than either controls or other patients with high cell loss.

In conclusion, our results do not support the hypothesis that patients undergoing cataract surgery who are at particular risk of developing postoperative bullous keratopathy may be differentiated on the basis of their preoperative or early postoperative endothelial cell morphology. We believe that any single measure of the corneal endothelium, whether it be of cell density or morphology, has limited potential as a predictor of outcome. Data from this study presented elsewhere suggest that the development of bullous keratopathy after cataract surgery may best be predicted by careful longitudinal observation of rate of endothelial cell loss.[15]

This study was supported by the National Eye Institute Grant No. EY 02677-06. We thank Celia Tagari for writing the digitisation program, Linda Wood for helping with the digitisation and preparing the paper, and Don Barbour for the photographic work.

References

1 Taylor DM, Atlas BF, Romanchuk KG, Stern AL. Pseudophakic bullous keratopathy. *Ophthalmology* 1983; **90**: 19–24.

2 Smith RE, McDonald HR, Nesburn AB, Minckler DS. Penetrating keratoplasty: changing indications, 1947–1978. *Arch Ophthalmol* 1980; **98**: 1226–9.

3 Rao G, Aquavella J, Goldberg S, Berk S. Pseudophakic bullous keratopathy: relationship to pre-operative corneal endothelial status. *Ophthalmology* 1984; **91**: 1135–40.

4 Oxford Cataract Treatment and Evaluation Team. I. Cataract surgery: interim results and complications of a randomised controlled trial. *Br J Ophthalmol* 1986; **70**: 402–10.

5 Price NC, Cheng H. Contact and non-contact specular microscopy. *Br J Ophthalmol* 1981; **65**: 568–74.

6 Cheng H, Jacobs PM, McPherson K, Noble MJ. Precision of cell density estimates and endothelial cell loss with age. *Arch Ophthalmol* 1985; **103**: 1478–81.

7 Bourne WM. Morphologic and functional evaluation of the endothelium of transplanted human cornea. *Trans Am Ophthalmol Soc* 1983; **81**: 403–50.

8 Alanko H. Microcomputer analysis for corneal endothelial cell morphology. *Acta Ophthalmol (Kbh)* 1983; **61**: 229–39.

9 Sawa M, Tanishima T. The morphometry of the human corneal endothelium and follow up of postoperative changes. *Jpn J Ophthalmol* 1979; **23**: 337–50.

10 Waring GO, Krohn MA, Ford GE, Harris RR, Rosenblatt LS. Four methods of measuring human corneal endothelial cells from specular micrographs. *Arch Ophthalmol* 1980; **98**: 848–55.

11 Stefanson A, Mueller O, Sundmacher R. Non-contact specular microscopy of the normal corneal endothelium; a statistical evaluation of morphometric parameters. *Graefes Arch Klin Exp Ophthalmol* 1982; **218**: 200–5.

12 Oxford Cataract Treatment and Evaluation Team. III. Long term corneal endothelial cell loss after cataract surgery. *Arch Ophthalmol* 1986; **104**: 1170–5.

13 Bourne WM, Brubaker RF, O'Fallon M. Use of air to decrease endothelial cell loss during intraocular lens implantation. *Arch Ophthalmol* 1979; **97**: 1473–5.

14 Schultz RD, Matsuda M, Yee RW, Edelhauser HF, Schultz KJ. Corneal endothelial changes in type I and type II diabetes mellitus. *Am J Ophthalmol* 1984; **98**: 401–10.

15 Bates AK, Cheng H, Hiorns RW. Pseudophakic bullous keratopathy: relationship with endothelial cell density and use of a predictive cell loss model. *Curr Eye Res* 1986; **5**: 363–6.

Accepted for publication 30 March 1987.

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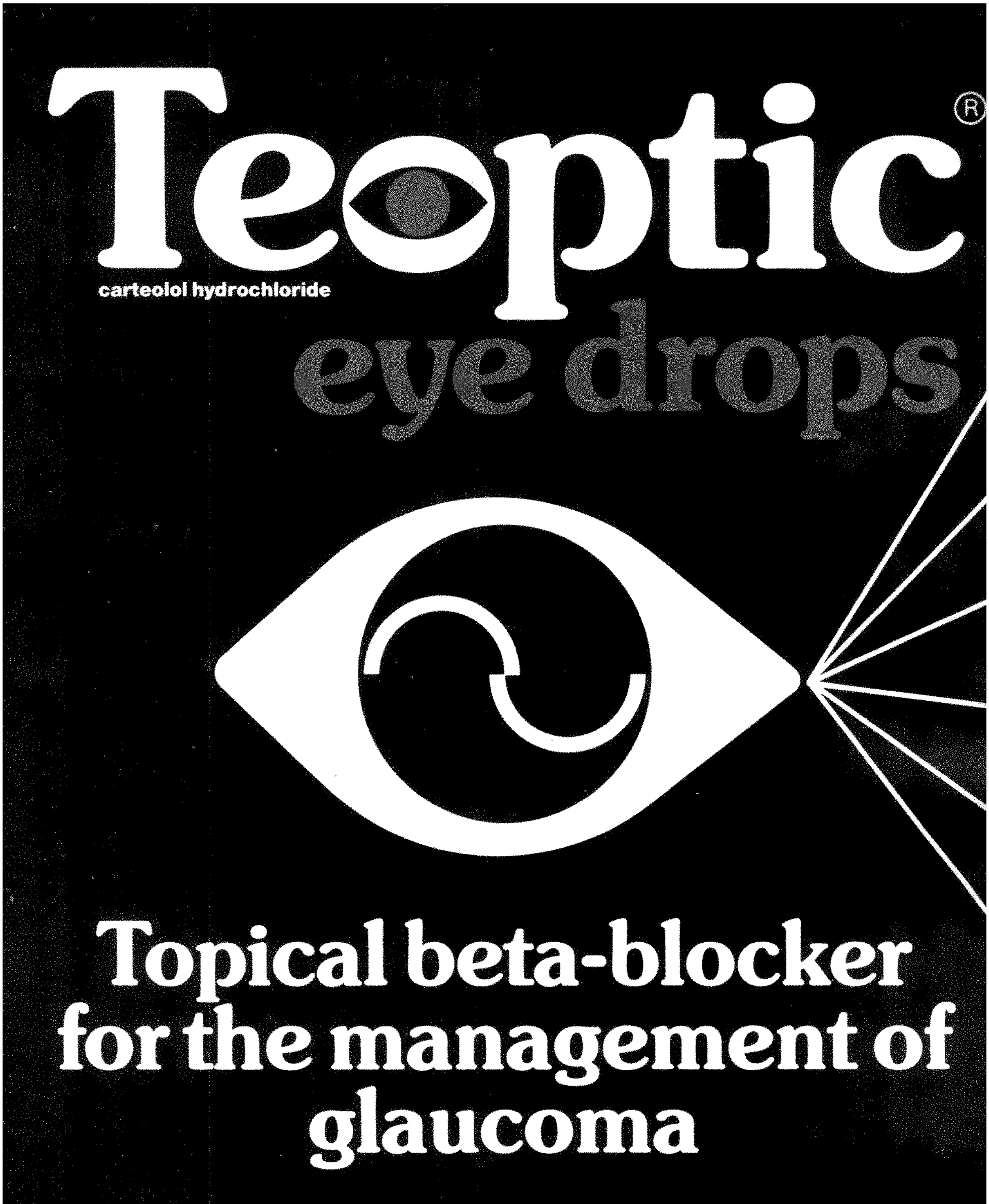

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British Journal of Ophthalmology, 1988, 72, 413–419

Viscodelamination at the vitreoretinal juncture in severe diabetic eye disease

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From the Surgical Vitreoretinal Unit, Moorfields Eye Hospital, London

SUMMARY Injection of 1% methylcellulose or 1% sodium hyaluronate (Healonid) was used to separate attached vitreous cortex and fibrovascular epiretinal membranes from the retina in 40 eyes undergoing closed microsurgery for severe diabetic eye disease. The viscodelamination technique was of great value in elevating vitreous cortex or sparsely vascularised epiretinal membranes, especially in eyes with combined traction and rhegmatogenous retinal detachment. However, bleeding from or tearing of the retina limited the usefulness of this technique in the surgery of highly vascularised and adherent membranes, as in eyes with table-top traction retinal detachment. Recurrent epiretinal membrane proliferation was seen in some eyes postoperatively.

Proliferative diabetic retinopathy (PDR) is characterised by outgrowth of new blood vessels and fibroblasts into the scaffold provided by attached cortical vitreous gel. The blinding sequelae of PDR —namely, retinal detachment and vitreous haemorrhage—result either from contraction of such fibrovascular epiretinal membranes (ERMs) or from avulsion of the edges of the membranes during posterior vitreous detachment (PVD) with retinal break formation or rupture of new vessels. The twin strategies underlying the surgical treatment of PDR complications are, firstly, reduction in the stimulus to vasoproliferation (for example, by means of scatter endophotocoagulation of ischaemic retina[1]), and secondly removal of postbasal vitreous cortex together with any fibrovascular tissue contained therein.[2] Technical difficulties may arise, however, if the fibrovascular ERMs are excessively adherent or if the vitreous cortex remains extensively attached to the retina.[3,4] Stenkula and Tornquist described methods of elevating ERMs from the retina using sodium hyaluronate.[5]

The purpose of this paper is to report our experience of using viscous fluids to separate cortical vitreous and ERMs from the retinal surface ('viscodelamination'[6]) during closed microsurgery for severe diabetic eye disease.

Material and methods

Between 1984 and 1986 a viscodelamination technique was employed during closed microsurgery for complications of PDR in 40 eyes of 38 patients in the Surgical Vitreoretinal Unit at Moorfields Eye Hospital, London. In the majority of procedures (28 eyes) 1% methylcellulose (formulated in Moorfields' pharmacy) was used; methylcellulose at 2% concentration (as used in anterior segment surgery) had been found to be excessively difficult to aspirate from the eye after viscodelamination. In the remaining 12 eyes sodium hyaluronate 1% (Healonid) was used.

Eyes suitable for viscodelamination were usually identified during preoperative ophthalmoscopic or ultrasonic examination by paying careful attention to the extent of PVD. Eyes with macular traction retinal detachment (10 eyes) or combined traction and rhegmatogenous detachment (18 eyes) *but with minimal or limited PVD* were specially selected for viscodelamination (Fig. 1). In a further seven eyes viscodelamination was employed primarily to aid scissors dissection (segmentation or delamination) of widespread fibrovascular ERMs causing 'table-top' traction retinal detachment. It was relatively unusual for extensive non-separation of the vitreous cortex to accompany vitreous haemorrhage without significant retinal detachment (five eyes).

Healonid 1% (prepacked in a 2 ml syringe) or 1%

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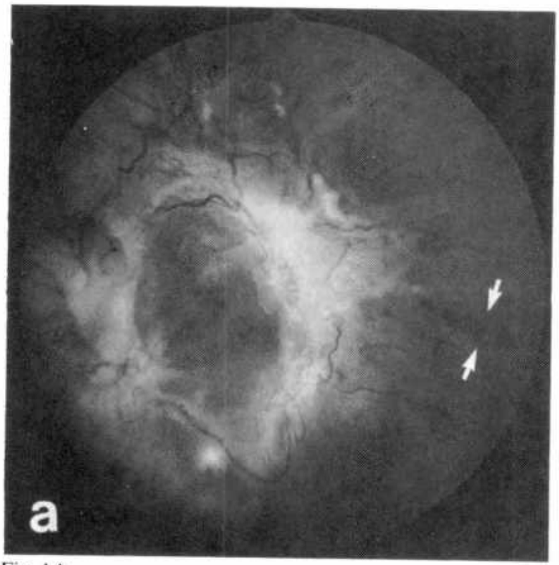


Fig. 1A

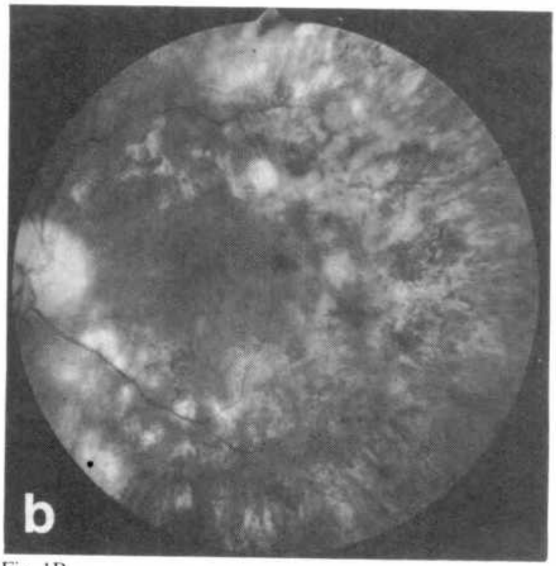


Fig. 1B

Fig. 1 *Two eyes with combined traction and rhegmatogenous retinal detachment treated by vitrectomy, viscodelamination, and gas tamponade.* (A) *Preoperative fundus photograph with retinal break arrowed; acuity=3/60.* (B) *Same eye as (A) one month postoperatively; acuity=6/12.* (C) *Preoperative fundus photograph (note macular hole); acuity=hand motion.* (D) *Same eye as (C) two months postoperatively; acuity=4/60.*

methylcellulose in a 5 ml syringe was connected via flexible tubing to a 20 gauge cannula with a bent tip ('hockey stick'). After central vitrectomy by the standard three-port system popularised by Charles,[7] 1–3 ml of viscous fluid was injected between attached cortical vitreous gel and the retina via a pre-existing hiatus in an area of detached vitreous cortex or following creation of a 1 mm diameter hole in attached or detached cortex by means of a microvitreoretinal blade or the suction cutter (Fig. 2). The infusion fluid which was thus displaced anteriorly sometimes escaped from the eye round the fibreoptic endoilluminating probe or injection cannula; alternatively, fluid returned up the infusion cannula and

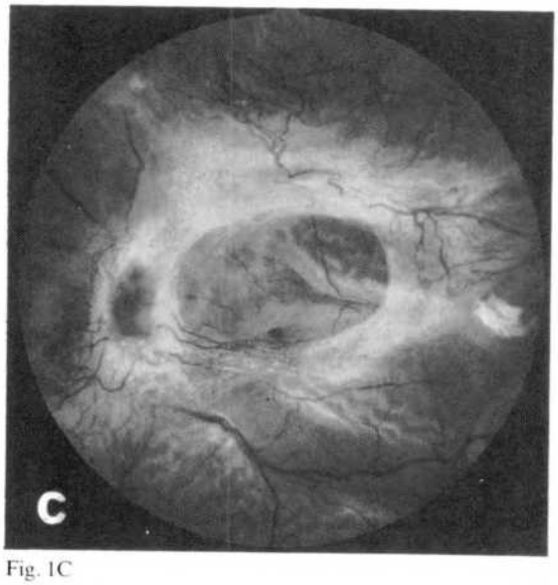


Fig. 1C

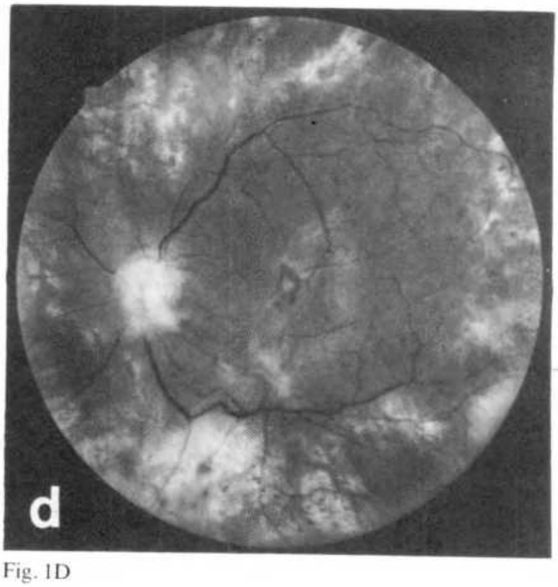


Fig. 1D

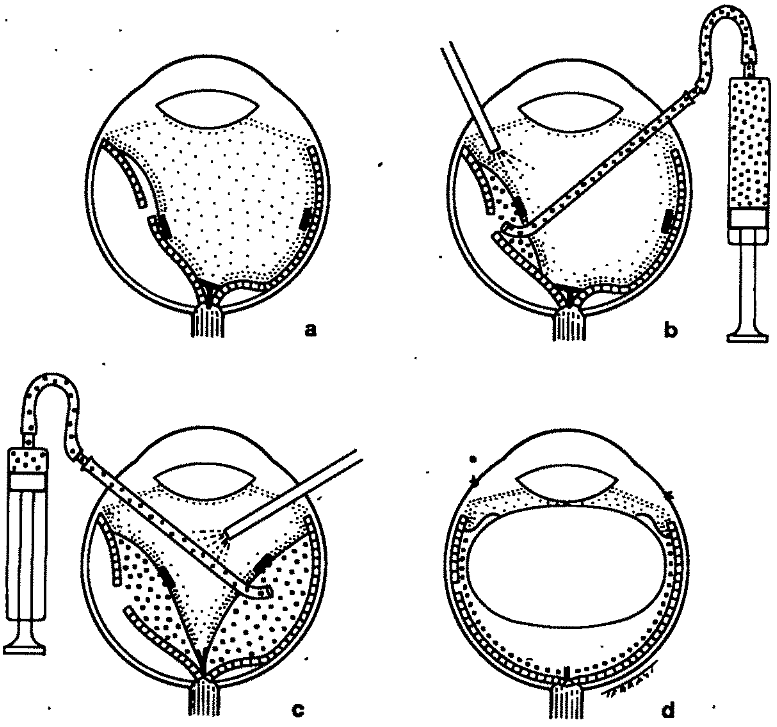


Fig. 2 *Diagrams of the viscodelamination technique.* (a) *Combined traction and rhegmatogenous retinal detachment with vitreous cortex extensively attached.* (b) *Outset of viscous injection after central vitrectomy.* (c) *Completion of en bloc viscodelamination except at optic disc.* (d) *Internal tear closure by gas after completion of vitrectomy and aspiration of viscous injectate.*

tubing or was intermittently released from one of the two superior sclerotomies in response to ocular hypertension. The speed and volume of injection of viscous material was controlled by verbal instructions to the surgical assistant, who held the syringe in one hand while keeping the fundus-viewing infusion contact lens in suitable position on the cornea with his other hand.

Viscodelamination was accompanied by limited blunt mechanical separation of vitreous cortex with the curved cannula. In some eyes further holes were made in the vitreous cortex to permit complete postbasal separation of the vitreous through 360°, while traction on persisting adhesions between the retina and the ERMs was minimised. Local circumcision of vitreoretinal adhesions or scissors segmentation or delamination of membranes was carried out during, and/or at the completion of, the retrohyaloid viscous injection, while the cortical vitreous 'cone' remained virtually intact.

With the suction cutter vitrectomy was then completed (including removal of ERMs within the visco-elevated posterior vitreous cortex), and most of the retrohyaloid viscous injectate was aspirated. However, bipolar diathermy of bleeding points often revealed a persistent viscous layer on the retinal surface as indicated by temporary opacification during diathermy. Thereafter further measures to stabilise the posterior segment included internal drainage of subretinal fluid, fluid/gas or fluid/silicone oil exchange (Figs. 3, 4) and focal or scatter endophotocoagulation. The viscous fluid was not used primarily to achieve internal closure of retinal breaks. In view of the potential risk of reparative epiretinal fibrosis it was considered especially important to remove all viscous fluid from eyes into which silicone oil was subsequently injected (16 eyes).

The outcome of surgery was evaluated at six months postoperatively in all cases. Complete retinal reattachment or only localised, stable, extramacular traction retinal detachment was regarded as a successful anatomical outcome.

Results

In all but four eyes complete separation of non-vascularised postbasal vitreous cortex was achieved, so that after vitrectomy no connection persisted between any residual epiretinal fibrovascular tissue and the vitreous base. Indeed in most eyes no fibrovascular tissue remained except at the optic disc (Figs. 1–4). On only one occasion was injected viscous material identified in the subretinal space; otherwise the progressive separation of vitreous cortex and retina was associated with apparent flat-

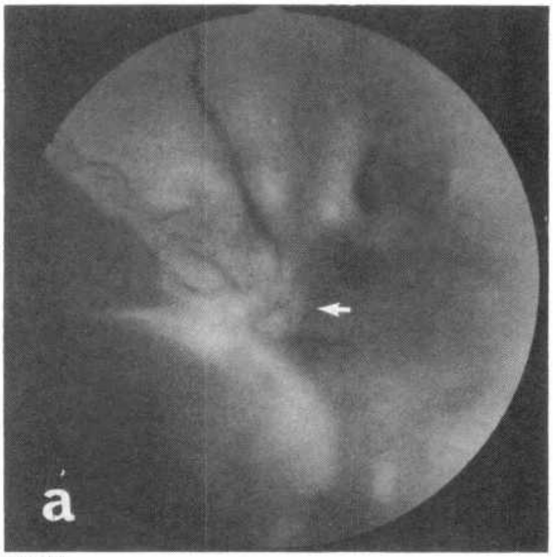


Fig. 3A

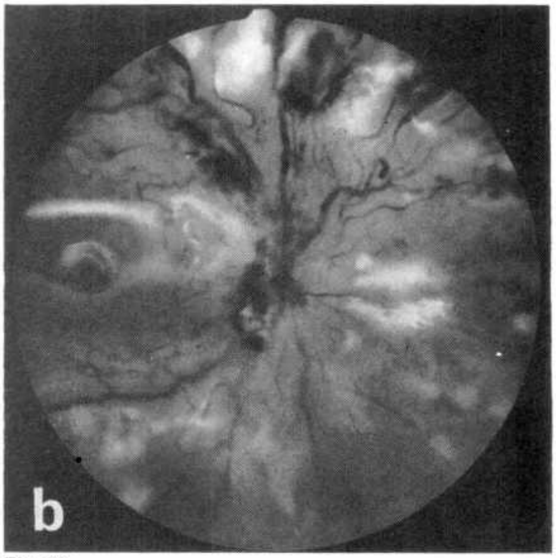


Fig. 3B

Fig. 3 *Active proliferative retinopathy treated by vitrectomy, viscodelamination, endolaser, and silicone oil exchange.* (A) *Preoperative fundus photograph showing oedematous detached retina above optic disc (arrow) and dense premacular retrohyaloid haemorrhage; acuity=hand motion.* (B) *Same eye as (A) two days postoperatively.* (C) *Same eye nine months later and following removal of silicone oil; acuity=6/18.*

tening of the retina. However, preretinal haemorrhage was frequent during viscodelamination owing to avulsion of the vascularised adhesions between the ERMs and the retina. Nevertheless the bleeding generally remained localised, and no difference was noted between Healonid 1% and methylcellulose 1% in respect of this intraoperative haemostasis or 'haemorrhage confinement'. Retinal tearing attributable to the viscodelamination technique was identified in 12 eyes (Table 1), while a retinal break near a surgical entry site (and possibly attributable to vitreous base herniation during the viscous injection) was found in four eyes at the end of the procedure.

No ocular hypertension or undue inflammation attributable to residual viscous injectate was evident postoperatively. A successful anatomical outcome (accompanied by visual improvement) was achieved in 28 of the 40 eyes (Table 1). Surgical failure reflected the development of macular distortion from reparative epiretinal fibrosis in two eyes, rubeotic glaucoma plus retro-silicone oil neovascularisation in one eye (Fig. 4), and combined traction and rhegmatogenous retinal redetachment in nine eyes.

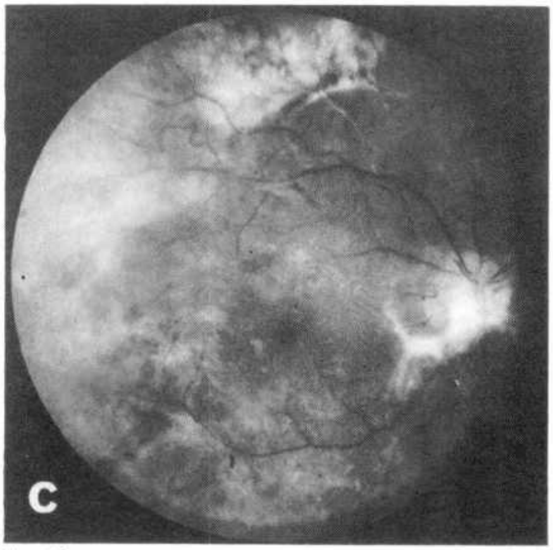


Fig. 3C

Table 1 *Results of viscodelamination in 40 eyes with PDR*

	Number of eyes	*Successful outcome*	*VDL-induced retinal breaks*
VH	5	5	1
TRD	10	8	3
CTRD	18	11	4
TTTRD	7	4	4
Totals	40	28	12

VH=vitreous haemorrhage. TRD=traction retinal detachment.
CTRD=combined traction and rhegmatogenous detachment.
TTTRD=table-top traction retinal detachment.
VDL=viscodelamination.

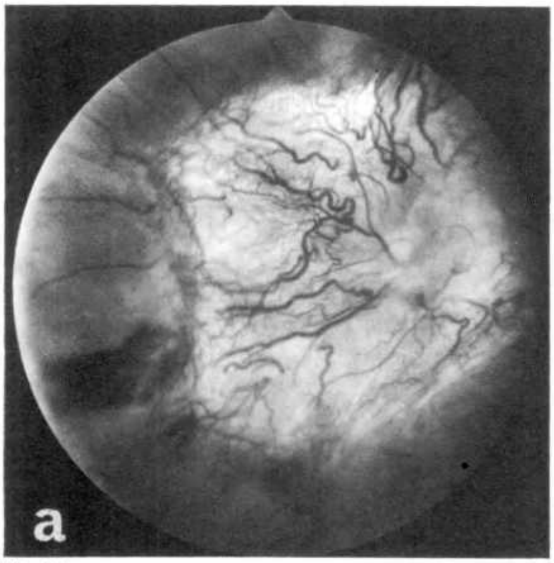


Fig. 4A

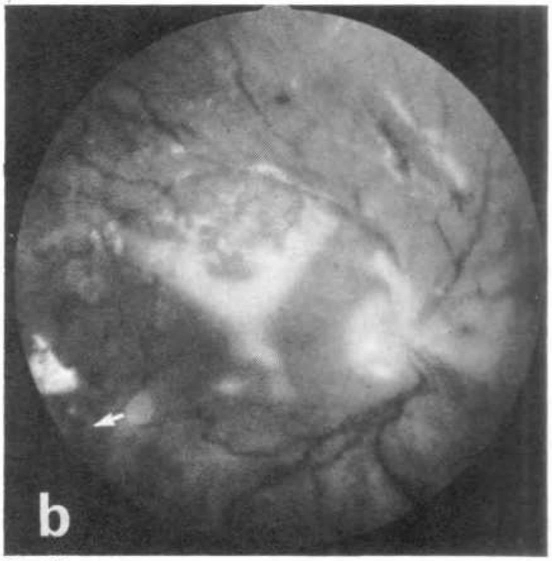


Fig. 4B

Fig. 4 *Table-top traction retinal detachment treated by vitrectomy, viscodelamination, and silicone oil exchange.* (A) *Preoperative fundus photograph; acuity=hand motion.* (B) *Same eye as (A) three days postoperatively (single retinal break arrowed).* (C) *Retro-silicone oil neovascularisation (arrow) one month later.*

In four of these nine eyes the presence of intravitreal silicone oil permitted 'rhegmatogenous confinement' of the detachment to an extramacular location, and all four had improved vision six months postoperatively.

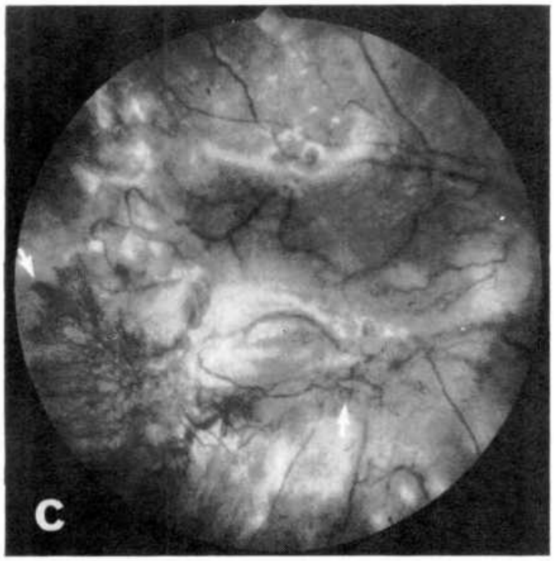


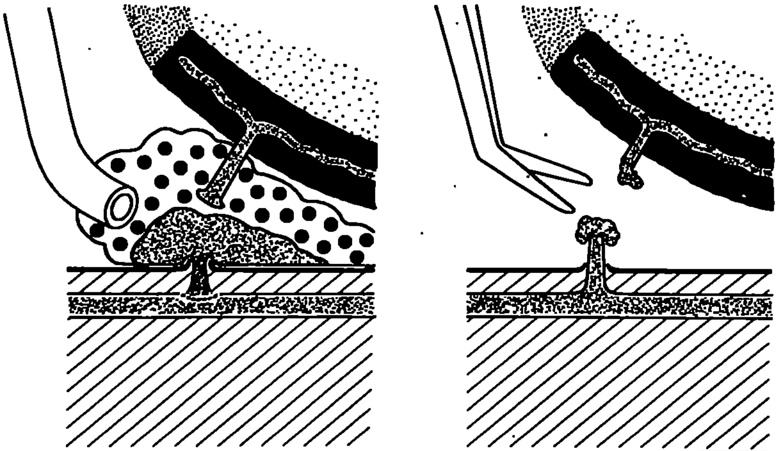
Fig. 4C

Discussion

Isolation of postbasal fibrovascular foci from the vitreous base by vitrectomy-circumcision reduces the tendency to postoperative rebleeding or retinal redetachment in PDR,[8] while removal of all postbasal vitreous cortex usually prevents any further epiretinal neovascularisation.[2] Even if the vitreous cortex remains attached to the retina preoperatively, these fundamental objectives of diabetic vitrectomy can often be achieved using microscissors, microforceps, etc. Such mechanical vitreoretinal separation may be facilitated by cortical gel condensation or fibroglial invasion of the vitreous cortex, often accompanied by multiple focal areas of PVD.[9] Nevertheless viscodelamination of vitreous cortex from the retina often permits more rapid accomplishment of these objectives and is especially useful for separating multiple, sparsely vascularised ERMs in the midperiphery of phakic eyes. It has proved most valuable in eyes with combined traction and rhegmatogenous retinal detachment (in which separation of extensive acellular cortical vitreous from detached, ischaemic, and atrophic retina would otherwise have presented technical difficulties—Figs. 1, 2), and also in eyes with dense premacular retrohyaloid haemorrhage[10,11] (Fig. 3). However, the viscodelamination technique carries with it a significant risk of retinal breaks, which are especially likely to arise when attempts are made to elevate extremely adherent fibrovascular ERMs. Recourse to scissors delamination is thus essential if viscous membranoretinal separation does not readily occur.

Intraoperative haemorrhage and fibrin clot forma-

Fig. 5 *Diagrams comparing viscodelamination (left) and scissors delamination (right) of fibrovascular epiretinal membrane; note avulsion of vascularised outgrowth and bleeding from side puncture of retinal vein during viscodelamination, and transection of vascularised outgrowth by scissors delamination.*



tion is a serious risk in all eyes with highly vascularised epiretinal membranes whatever technique is employed. In our experience, however, bleeding is much more problematic if a vascularised outgrowth is avulsed from the intraretinal circulation—for example, during membrane peeling, blunt mechanical delamination, or viscodelamination—in contrast to its preretinal division during scissors delamination.[7] In the former case a 'side puncture' of a retinal vein is often slow to thrombose (Fig. 5), and haemostasis by diathermy necessitates retinal coagulation and retinal vascular occlusion. Scissors delamination of highly vascularised ERMs is a more appropriate technique, since the retinal cut end of the outgrowth seldom bleeds profusely (Fig. 5), or it can be selectively diathermised with minimal damage to the underlying retina. For those reasons we have now virtually abandoned the use of viscodelamination for removal of highly vascularised ERMs—for example, in table-top traction retinal detachment.

At the outset of this study we had expected that the relatively atraumatic interfacial separation of vitreous and retina by means of a viscous injection would prevent recurrence of ERMs postoperatively.[6,12] However, even in eyes where vitreoretinal separation was achieved entirely by viscodelamination (unaccompanied by retinal break formation, haemorrhage, or recourse to silicone oil injection) reparative epiretinal fibrosis sometimes developed. Notwithstanding a possible role of residual preretinal viscous fluid in this process, but as is also the case after epimacular membrane peeling,[13,14] membrane recurrence appears to be related to the underlying disease,[15] in this case ischaemic diabetic retinopathy. Moreover, when such an eye contains silicone oil, recurrent epiretinal *neovascularisation* may occur behind the oil globule despite complete prior removal of the cortical vitreous scaffold by viscodelamination (Fig. 4). This remarkable phenomenon may reflect increased retinal production of vasoproliferative factors in some silicone oil filled diabetic eyes because of reduced oxygen diffusion from the vitreous cavity into ischaemic areas of retina (Landers R, personal communication, 1986). Such diffusion otherwise appears to limit the damage resulting from retinal vascular non-perfusion.[16,17] Thus the use of viscous fluids in diabetic vitrectomy, whether an aqueous solution or silicone oil,[12] gives occasion for both tangible benefits and significant complications.

We are indebted to Miss Heather Lucas for secretarial assistance, to Mr K Sehmi for the clinical photographs, and to Mr T Tarrant for the diagrams.

References

1 Ficker LA, Passani F, Leaver PK, McLeod D. Xenon-arc endophotocoagulation during vitrectomy for diabetic vitreous haemorrhage. *Graefs Arch Clin Exp Ophthalmol* 1986; **224:** 423–7.

2 Michels RG. Vitrectomy for complications of diabetic retinopathy. *Arch Ophthalmol* 1978; **96:** 237–46.

3 Blankenship GW. Preoperative prognostic factors in diabetic pars plana vitrectomy. *Ophthalmology* 1982; **89:** 1246–9.

4 Barrie T, Feretis EB, Leaver PK, McLeod D. Closed microsurgery for diabetic traction macular detachment. *Br J Ophthalmol* 1982; **66:** 754–8.

5 Stenkula S, Tornquist R. Use of Healon in vitrectomy and difficult retinal detachments. In: Miller D, Stegman R, eds. *Healon (sodium hyaluronate): a guide to its use in ophthalmic surgery.* New York: Wiley, 1983: 207–21.

6 Barry PJ, Hiscott PS, Grierson I, Marshall J, McLeod D. Reparative epiretinal fibrosis after diabetic vitrectomy. *Trans Ophthalmol Soc UK* 1985; **104:** 285–96.

7 Charles S. *Vitreous microsurgery.* Baltimore, London: Williams and Wilkins, 1981.

8 Irvine AR. Indications for vitrectomy via the pars plana. *Trans Ophthalmol Soc UK* 1975; **95:** 436–43.

9 Faulborn J, Bowald S. Microproliferations in proliferative diabetic retinopathy and their relationship to the vitreous: corresponding light and electron microscopic studies. *Graefes Arch Clin Exp Ophthalmol* 1985; **223:** 130–8.

10 O'Hanley GP, Canny CLB. Diabetic dense premacular haemorrhage: a possible indication for prompt vitrectomy. *Ophthalmology* 1985; **92:** 507–11.

11 Ramsay RC, Knobloch WH, Cantrill HL. Timing of vitrectomy for active proliferative diabetic retinopathy. *Ophthalmology* 1986; **93:** 283–8.

12 McLeod D. Silicone-oil injection during closed microsurgery for diabetic retinal detachment. *Graefes Arch Clin Exp Ophthalmol* 1986; **224:** 55–9.

13 Hiscott PS, Grierson I, McLeod D. Natural history of fibrocellular epiretinal membranes: a quantitative, autoradiographic, and immunohistochemical study. *Br J Ophthalmol* 1985; **69:** 810–23.

14 Margherio RR, Cox MS, Trese MT, Murphy PL, Johnson J, Minor LA. Removal of epimacular membranes. *Ophthalmology* 1985; **92:** 1075–82.

15 McLeod D, Hiscott PS, Grierson I. Age-related cellular proliferation at the vitreoretinal juncture. *Eye* 1987; **1:** 263–81.

16 McLeod D. Retinal ischaemia, disc swelling and axoplasmic transport. *Trans Ophthalmol Soc UK* 1976; **96:** 313–6.

17 McLeod D, Marshall J, Kohner EM, Bird AC. The role of axoplasmic transport in the pathogenesis of retinal cotton-wool spots. *Br J Ophthalmol* 1977; **61:** 177–91.

Accepted for publication 15 April 1987.

British Journal of Ophthalmology, 1988, 72, 420–423

Intraocular infestation by the reindeer warble fly larva: an unusual indication for acute vitrectomy

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SUMMARY A case of ophthalmomyiasis interna posterior (OIP) caused by the larva of the Reindeer warble fly is reported. The larva was initially found intraretinally in the inferior parts of the fundus. From this position it moved into the macula lutea within two days, causing decreased visual acuity. Acute vitrectomy was performed and the larva was removed through a retinotomy. About two months afterwards a small retinal detachment appeared near the ora serrata, where the larva had entered the eye. The retina was reattached with a scleral buckling procedure. The patient regained most of his vision postoperatively. Pars plana vitrectomy is a safe procedure and we consider that in any case of OIP, with a living larva in the eye, acute vitrectomy should be considered, since the larva may damage vital parts of the eye. Furthermore, the site of entrance should be treated with photocoagulation to prevent retinal detachment.

The reindeer is practically the only animal host for the reindeer warble fly (*Oedemagena tarandi*). However, it has been observed that the fly often deposits eggs in the hair of humans, and it has occasionally been reported as the cause of human myiasis. This condition may be more commoner than the literature suggests, because the fly is widely distributed in the northern parts of Europe and America and the infestation might pass without any ocular symptoms.[1]

There are two kinds of human myiasis, ophthalmic and cutaneous. Hatching occurs four to seven days after the eggs are deposited, and the larva reaches the skin by a short migration route and penetrates the tissues enzymatically. The larva may be found in the anterior (ophthalmomyiasis interna anterior) or the posterior parts (OIP) of the eye and migrate between these. Differentiation between the two conditions is justified because of considerable differences in treatment and prognosis. In OIP the larva is found in the vitreous, or intraretinally between the pigment epithelium and the neuroretina, or sometimes in the choroid.[3-4] Asymptomatic cases have been recognised by the accidental finding of a dead larva in the vitreous or through hypopigmented tracks with a characteristic appearance.[3,5] In the latter case the larva had left the eye to enter the next stage in its development.

Damage to vision is caused mechanically, by a toxin, or through a uveitis which may not respond to steroid treatment. Retinal detachment may also complicate the disease. In spite of this a conservative approach has been recommended when no immediate threat to the eye is apparent.[1] The following case shows that the development of the infestation is difficult to anticipate in that movements of the larva may cause damage to central parts of the fundus in a relatively short period of time.

Case report

At the beginning of September 1986 a 77-year-old man was found to have reduced visual acuity and vitreous floaters in the left eye. He had previously been in good health and had normal vision. He had been on vacation in Lappland, one of the northern provinces of Sweden, for a few weeks during the summer. The symptoms appeared about five weeks later. The visual acuity was 0·7 in the left eye on examination. Some small vitreous opacities were seen, but otherwise there were no signs of uveitis. Criss-crossing hypopigmented tracks accompanied by haemorrhages were observed in the fundus (Fig.

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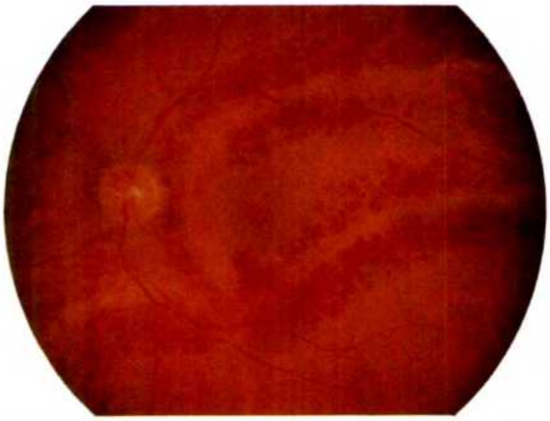

Fig. 1 *The posterior pole in the left eye. Hypopigmented subretinal tracks followed by retinal haemorrhages caused by a larva of the reindeer warble fly. The patient presented with visual floaters and reduced visual acuity (0·7).*

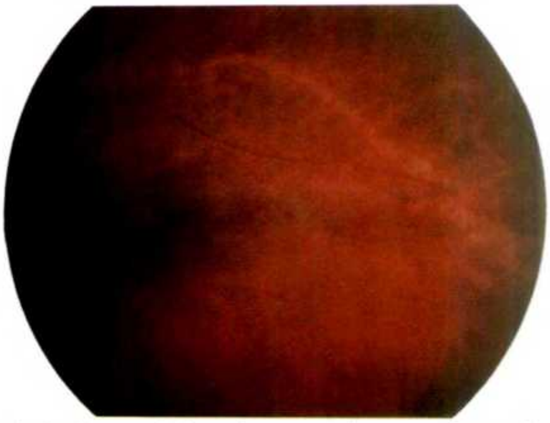

Fig. 3 *Presumed place of entrance in the temporal parts of the fundus near the ora serrata.*

1), and slightly below the inferior temporal vascular arcade a living subretinal larva was found (Fig. 2). This was later shown to be the first stage larva of the reindeer warble fly (*Oedemagena tarandi*). The larva measured approximately 3×1 mm. The tracks could be followed to a hyperpigmented spot near the ora serrata in the temporal parts of the fundus where the larva probably had entered the eye (Fig. 3). A general physical examination was negative and there were no disturbances in haematology or blood chemistry.

Removal of the larva through a pars plana vitrectomy was planned to be performed three days later. However, two days after the patient's admission to hospital the larva was found at the edge of the fovea centralis (Fig. 4), causing a subretinal haemorrhage with further deterioration of vision to 0·2. An urgent operation was performed and the larva removed alive through a retinotomy made by diathermy. Air was injected in the vitreous cavity in order to prevent retinal detachment. The retinotomy was sealed by argon laser photocoagulation the following day (Fig. 5). The haemorrhages resolved slowly in the central parts of the fundus leaving a slight retinal atrophy in the macula (Fig. 6). Vision improved to 0·6. A mild anterior uveitis was treated with local steroids and disappeared within a few weeks.

After about two months a small retinal detachment appeared in the temporal parts of the fundus near the ora serrata at the site where the larva had entered the eye. A small retinal break was seen. A scleral buckling procedure was carried out and the area

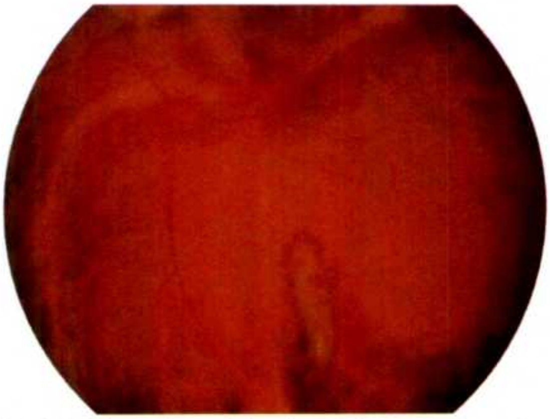

Fig. 2 *Subretinal larva below the inferior temporal vascular arcade.*

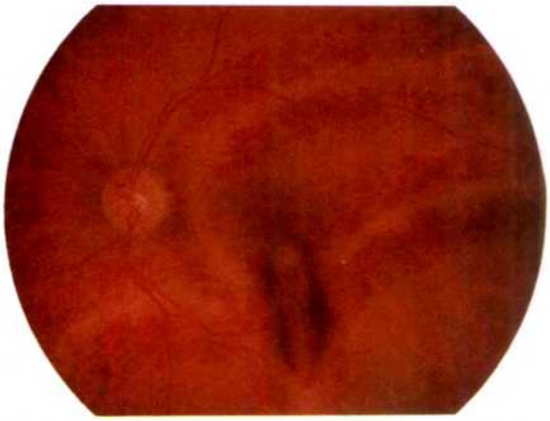

Fig. 4 *Within two days the larva moved to the edge of the fovea centralis causing a subretinal haemorrhage and further reduction of the visual acuity to 0·2.*

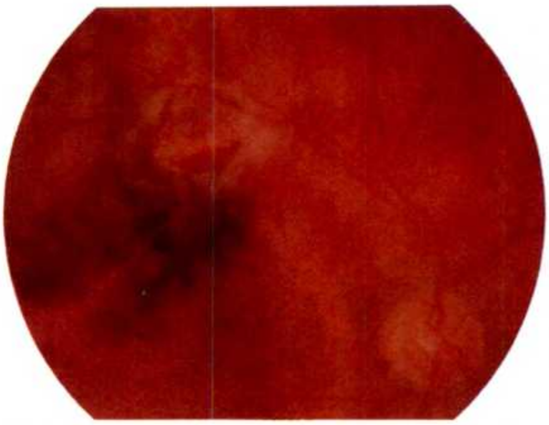

Fig. 5 *Fundus after removal of the larva. The edges of the retinotomy have been sealed by argon laser photocoagulation.*

treated by cryopexy. The retina became reattached and healed quickly. Central vision was not harmed by this complication.

Discussion

Syrdalen *et al.*[1] have suggested some guidelines for the treatment of OIP. According to these, the only indication for removal is when a dead larva in the vitreous causes an inflammatory reaction which does not respond to steroids. If there is no inflammation, the larva should be watched inside the eye and the development followed. A living subretinal larva should be destroyed with photocoagulation if outside the macular area, When the reindeer warble fly is the cause of OIP, it is the first larval stage that grows in the eye. This stage lasts about three months, and the larva may reach a length of 9 mm.[1]

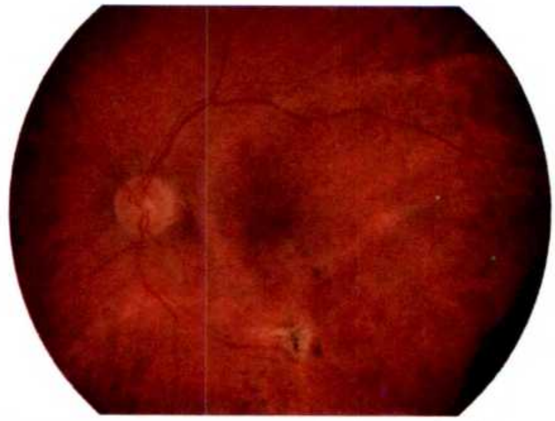

Fig. 6 *Four months later. Most of the haemorrhage has resolved. Some retinal atrophy is seen in the macula, but vision has improved to 0·6.*

When considering this and the history of our patient, we inferred that the larva had been in the eye for some weeks when it was discovered. The many tracks showed that it easily moved intraretinally, and it was probably not until it passed the central area, between the optic disc and the macula lutea, that the patient had some symptoms. When initially found, the larva was slightly below the inferior temporal vascular arcade. Within two days it moved to the edge of the fovea centralis. Any further movements would have caused irreversible damage to central vision. Thus it seems that any delay in adequate treatment entails an increased risk for the eye.

Destroying the larva with photocoagulation has been successful in some cases,[6] but there is always the risk of an ensuing uveitis or damage from the release of toxic substances. In the present case photocoagulation could not be performed when the larva was found in the macula because it would have impaired central vision. However, it might be argued that the patient should have been treated with photocoagulation when he was first seen.

Pars plana vitrectomy is a safe procedure with little risk of complications. In case of OIP the larva is relatively easy to remove from the vitreous[7] or, as in this case, through a retinotomy from the intraretinal space. Thus in our opinion all cases of OIP should alert the clinician to consider removal as soon as possible, because the situation may quickly change and vision be damaged.

A small rhegmatogenous retinal detachment developed after two months near the site where the larva had entered the eye. Slight hyperpigmentation without any visible vitreous traction or breaks had previously been observed in the area. In spite of this, it is obvious that retinal detachment might occur after a relatively long period of time. We assume that the larva caused retinal damage when it entered the eye. However, there is a possibility that the surgical procedure, when the larva was removed, might have contributed or been the sole cause of the detachment. But, since damage from the larva cannot be excluded, caution must be advocated, and photocoagulation of the place of entrance should always be considered.

References

1 Syrdalen P, Nitter T, Mehl R. Ophthalmomyiasis interna posterior: report of a case caused by the reindeer warble fly larva and review of previous reported cases. *Br J Ophthalmol* 1982; **66:** 589–93.

2 Slusher MM, Holland WD, Weaver RG, Tyler ME. Ophthalmomyiasis interna posterior. *Arch Ophthalmol* 1979; **97:** 885–7.

3 Gass JDM, Lewis RA. Subretinal tracks in ophthalmomyiasis. *Arch Ophthalmol* 1976; **94:** 1500–5.
4 Mason GI. Bilateral ophthalmomyiasis interna. *Am J Ophthalmol* 1981; **91:** 65–70.
5 Ziemianski MC, Lee Ky, Sabates FN. Ophthalmomyiasis interna. *Arch Ophthalmol* 1980; **98:** 1588–9.
6 Forman AR, Cruess AF, Benson WE. Ophthalmomyiasis treated by argon-laser photocoagulation. *Retina* 1984; **4:** 163–5.
7 Rapoza PA, Michels RG, Semeraro RJ, Green WR. Vitrectomy for excision of intraocular larva. *Retina* 1986; **6:** 99–104.

Accepted for publication 23 April 1987.

British Journal of Ophthalmology, 1988, **72**, 424–427

Neonatal Graves' disease

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SUMMARY A newborn boy was noted by his mother to have a prominent left eye at birth, but an eye examination was delayed until age 7 months, at which time his ophthalmologist diagnosed exophthalmos. Computed tomography was interpreted as showing mild, diffuse, optic nerve thickening bilaterally suggestive of optic nerve gliomas. Subsequent examination in our clinic revealed pseudoproptosis secondary to retraction of the left upper eyelid. Magnetic resonance imaging demonstrated normal orbital structures. The mother was noted to be clinically hyperthyroid, and abnormal thyroid function tests confirmed the diagnosis. Although the infant was euthyroid, neonatal Graves' ophthalmopathy was diagnosed. He was managed by close observation while his mother was treated for her hyperthyroidism.

Neonatal or congenital Graves' disease has been described as a rare disorder of infants born to mothers who have been hyperthyroid during pregnancy.[1] The clinical features of this disease in the newborn range from transient subtle signs of hyperthyroidism lasting four to six months to a severe protracted disorder that significantly affects growth, development, and intellectual and emotional maturation.[1-3] The pathogenesis of congenital Graves' disease is unknown, but it is postulated that it is secondary to transplacental transmission of an antithyroid antibody in a genetically preselected population.[1,3,4]

Ophthalmologically the affected newborn baby may present with exophthalmos and/or lid retraction. If congenital Graves' disease is suspected, thyroid function tests in both the patient and mother are indicated, and appropriate systemic treatment should be promptly instituted for this potentially serious disease.[1-3]

Case report

A newborn boy was noted by his mother to have a prominent left eye at birth (Fig. 1). The appearance of the left eye did not change over the ensuing months, and the child was finally examined by an ophthalmologist at another institution at age 7 months. Clinical findings at that time included proptosis and questionable amblyopia of the left eye (OS). Computed tomography of the orbits was interpreted as showing diffusely thickened optic nerves bilaterally, suggestive of optic nerve gliomas.

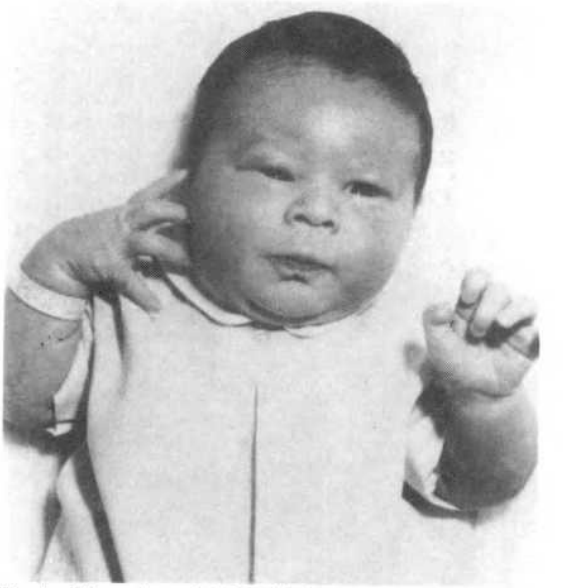

Fig. 1 *The patient at birth with left upper lid retraction.*

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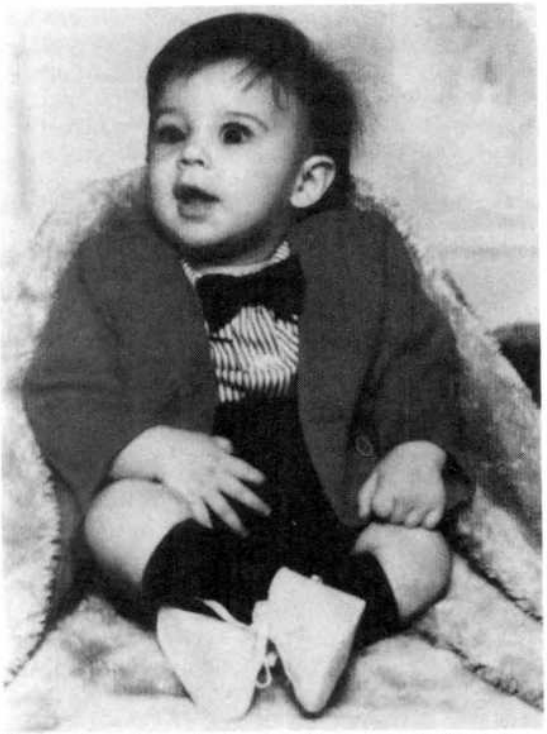

Fig. 2 *At age 9 months there is still no apparent change in clinical features.*

We examined the child at 9 months of age, at which time he could fixate and follow small objects with each eye, and the pupils were equal and found without an afferent defect. There was 2 mm retraction of the left upper eyelid (Fig. 2), which remained in an elevated position on downgaze. There was no exophthalmos or contralateral blepharoptosis. The extraocular movements showed slightly deficient upgaze OS but were otherwise normal.

The cycloplegic refraction revealed a +2·00 sphere in both eyes, and the fundi and optic discs were normal, with no evidence of disc oedema, optic atrophy, or opticociliary shunt vessels. General physical examination was completely normal. The patient was the product of a normal pregnancy, labour, and delivery. The family history was remarkable for diabetes mellitus and thyroid disease in the mother and several relatives. The patient's mother had recently been diagnosed as having hyperthyroidism characterised by a diffusely enlarged goitre, resting tremor, resting pulse of 130, and widened pulse pressure of 145/70 mmHg.

Table 1 *Thyroid studies of the child and his mother*

Test	*Results*		
	Child	*Mother*	*Normals*
T3 RIA	170	512	65–195 mg/dl
T3 uptake	38	55	35–45%
T4	9·4	*	5·5–13·5 mcg/dl
Thyroid stimulating immunoglobin (TSI)	<2·0	7·9	<2·0 mIU eq/ml
Antithyroid antibody	*	1:40	<1:20

*Test not performed.
mg/dl = Milligrams/decilitre. mcg/dl = Micrograms/decilitre.
mIU eq/ml = Microinternational units equivalent/millilitre.

Laboratory evaluation (Table 1) revealed entirely normal thyroid studies in the 9-month-old patient. Thyroid studies of the patient's mother disclosed significantly raised levels of triiodothyronine (T3), increased T3 uptake, and increased thyroid stimulating immunoglobulins (TSI). The antithyroid antibodies were likewise raised at 1:40.

The results of computed tomography of the orbit, which were interpreted at another institution as showing bilateral diffuse optic nerve gliomas, were subsequently interpreted by several neuroradiologists at our institution as being within normal limits (Fig. 3). A magnetic resonance imaging (MRI) scan of the orbits was performed on the patient and the findings were within normal limits, with no evidence of optic nerve glioma.

From the clinical and laboratory findings the diagnosis of neonatal Graves' ophthalmopathy was made. The young child was managed by observation alone and has remained without changes in his appearance at 10 months follow-up. The patient's mother has undergone appropriate treatment for hyperthyroidism.

Discussion

Hyperthyroidism is uncommon during childhood and adolescence, with an incidence of 3·8 cases per

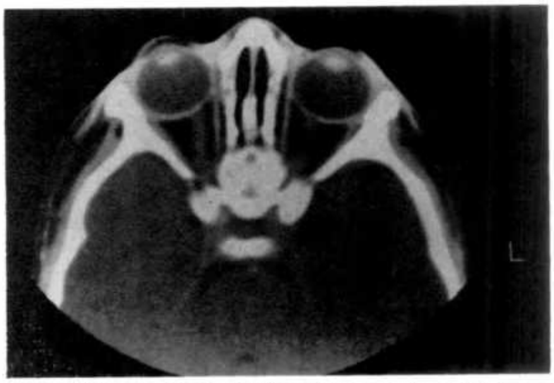

Fig. 3 *Computed tomography of the orbits demonstrate normal optic nerves in our 10-month-old patient.*

100 000 population per year.[5,6] The causes of childhood hyperthyroidism are most commonly acquired Graves' disease and much less commonly neonatal or congenital Graves' disease, thyroid adenomas and carcinomas, lymphocytic thyroiditis, and polyostotic fibrous dysplasia (McCune-Albright syndrome).[2]

Neonatal Graves' disease was first described by Ochsner and Thompson in 1910.[7] They reported an exophthalmic boy born to a mother who had exophthalmos and a goitre. Since this initial report several cases have been reported, primarily in the endocrinology literature.

Hollingsworth and coworkers[3] suggested that two types of congenital Graves' disease exist. The first and more common type occurs in infants born to mothers with active or recently active Graves' disease. The disease in the newborn baby tends to be mild, transient, and resolves at about 3 to 6 months of age without sequelae or recurrence. The second and less common type of congenital Graves' disease usually has its onset in early infancy, though it may be present at birth. There is usually a family history of Graves' disease, but the mother may or may not have Graves' disease. This type tends to persist with late sequelae of premature fusion of the cranial sutures, microcephaly, short stature, and mental and emotional retardation.

Early clinical features of both types are similar. The patients may be premature and of low birth weight. Periorbital oedema, lid retraction, exophthalmos, and goitre are almost always present, and other manifestations include tachycardia, irritability, and polyphagia.[2]

Table 2 *Causes of lid retraction in children*

Location	*U/B*	*Aetiology*
A. CNS (dorsal midbrain)	B	Pinealoma
	B	Hydrocephalus
	B	Meningitis
	U	Cyclic oculomotor spasm
	U	Duane's syndrome
B. Peripheral nerve	U	Aberrent regeneration III nerve
	B	Overactive sympathetic system
	U	Marcus Gunn jaw winking phenomenon
C. Neuromuscular junction	B	Drugs—edrophonium chloride
	B	—prostigmine
	B	—succinylcholine
	U or B	—phenylephrine
	U	Unilateral ptosis with contralateral levator overaction (myasthenia)
D. Muscle	U or B	Thyroid
	B	Hyperkalaemic periodic paralysis
	B	Chronic systemic corticosteroid
	U	Congenital levator fibrosis
E. Non-specific	B	'Eye popping' of children in dark rooms

U = unilateral. B = bilateral.

There is significant variation in the severity of congenital Graves' disease. Some patients may have eye signs only without other signs of thyrotoxicosis, while others may have the spectrum of systemic findings of thyrotoxicosis. Hollingsworth and Mabry[1] reported a series of 74 neonates with congenital Graves' disease and noted that a surprisingly high percentage (16%) of these patients died either from prematurity, respiratory distress, or thyrotoxicosis. They emphasised the possible seriousness of this entity and pointed out that many of the fetuses die in utero.

Several theories exist as to the pathogenesis of neonatal Graves' disease.[1,4,8-10] The most widely accepted postulate is that it develops in an infant with a genetic predilection who has acquired one or several immunoglobulins from the mother via transplacental transmission. It is believed that these immunoglobulins may be antithyroid antibodies with enhancer and blocking agents that either stimulate or inhibit the activity of the antibody.[11]

The patient we report on seems to resemble the milder form of congenital Graves' disease with eye findings only, but his upper eyelid retraction has persisted longer than the typical three to six months. Others[11,12] have reported persistence of eye signs for more than one year.

It is sometimes difficult to distinguish eyelid retraction from exophthalmos, especially in restless children. Close attention to the movement of the eyelids, especially during duction movements, and careful exophthalmometry readings will usually differentiate between these two conditions. Bilateral and unilateral lid retraction can be seen in a variety of diseases[13,14] (Table 2). A complete history and examination of the neonate for each of these entities should be performed. In cases of suspected thyroid disease or myasthenia gravis the mother should also be examined. In our patient's mother the thyroid function tests were grossly abnormal, though the child's studies were within normal limits. This may be explained by the fact that the child presented at age 9 months, and most maternal antibodies are not present in the neonate after 3 to 5 months.[11] We postulate that in the first few months of life our patient may have had raised thyroid hormones.

Treatment of neonatal Graves' disease includes a combination of antithyroid drugs, preferably propylthiouracil and iodine, and β-adrenergic blockers when needed.[2,15] Rarely thyroidectomy has been needed after medicinal failure. Our patient had no evidence of thyrotoxicosis at the time when he presented to us, so therapy consisted of observation only.

The ophthalmologist should be aware of this unusual cause of eyelid retraction in the newborn and recognise the need for prompt paediatric and endocrinological care of the patient and mother.

This work was supported by a grant from Fight for Sight, Inc, New York to the Fight for Sight Children's Eye Center of Wills Eye Hospital, Philadelphia, Pennsylvania.

References

1 Hollingsworth DR, Mabry CC. Congenital Graves' disease. In: Fischer DA, Burrow GN, eds. *Perinatal thyroid physiology.* New York: Raven, 1975: 163.

2 Howard CP, Hayles AB. Hyperthyroidism in childhood. *J Clin Endocrinol Metab* 1978; 7: 127–43.

3 Hollingsworth DR, Mabry CC, Eckerd JM. Hereditary aspects of Graves' disease in infancy and childhood. *J Pediatr* 1972; **81:** 446–59.

4 Green WL. Humoral and genetic factors in thyrotoxic Graves' disease and neonatal thyrotoxicosis. *JAMA* 1976; **235:** 1149–50.

5 Furszyfer J, Kurland LT, McConahey WM, Elveback LR. Graves' disease in Olmstead County, Minnesota 1935 through 1967. *Mayo Clin Proc* 1970; **45:** 636–44.

6 Zimmerman D, Hayles AB. Hyperthyroidism in childhood. *Pediatr Adolesc Endocrinol* 1985; **14:** 223–39.

7 Ochsner AJ, Thompson RL. *The surgery and pathology of the thyroid and parathyroid glands.* St Louis: Mosby, 1910: 192.

8 Gossage AAR, Munro DS. The pathogenesis of Graves' disease. *J Clin Endocrinol Metab* 1985; **14:** 299–330.

9 Zakarija M, McKenzie JM, Hoffman WH. Prediction and therapy of intrauterine and late-onset neonatal hyperthyroidism. *J Clin Endocrinol Metab* 1986; **62:** 368–71.

10 Zakarija M, McKenzie JM. Pregnancy-associated changes in the thyroid-stimulating antibody of Graves' disease and the relationship to neonatal hyperthyroidism. *J Clin Endocrinol Metab* 1983; **57:** 1036–40.

11 Keynes G. Obstetrics and gynaecology in relation to thyrotoxicosis and myasthenia gravis. *J Obstet Gynaecol* 1952; **59:** 173–82.

12 Givner I, Bruger M, Lowenstein O. Exophthalmos and associated ocular disturbances in hyperthyroidism. *Arch Ophthalmol* 1947; **37:** 211–9.

13 Sergott RC, Glaser JS. Graves' ophthalmopathy. A clinical and immunologic review. *Surv Ophthalmol* 1981; **26:** 1–21.

14 Martyn LJ. Pediatric neuroophthalmology. In: Harley RD, ed. *Pediatric ophthalmology.* Philadelphia: Saunders, 1983: 11, 12, 810–12.

15 Zimmerman D, Hayles AB. Treatment of Graves' disease in children. In: Mellinger JF, Stickler GB, eds. *Critical problems in pediatrics.* Philadelphia: Lippincott, 1983: 69–84.

Accepted for publication 23 April 1987.

British Journal of Ophthalmology, 1988, **72**, 428–431

A fatal case of necrotising fasciitis of the eyelid

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SUMMARY A fatal case of necrotising fasciitis in a 35-year-old man is described and the differential diagnosis and management discussed.

Necrotising fasciitis is a potentially fatal skin infection which is being increasingly recognised as an underdiagnosed condition. It requires prompt diagnosis, investigation, and treatment. Early surgical debridement is, in combination with suitable intravenous antibiotics, the mainstay of treatment.

Case report

In December 1985 a previously fit 35-year-old factory manager was referred by his general practitioner to the Casualty Department of the Southampton Eye Hospital with a 12-hour history of increasing redness and swelling of his right upper lid. He said that two days previously he had been poked in the same eye by his daughter (who had been playing with her guinea-pig) but that he had been symptomless until the day of presentation.

On examination he was febrile (38°C) and clearly unwell. His right eyelid was markedly erythematous, swollen, and tender, and there was a copious purulent discharge from the eye. The oedema and erythema extended to his temple as far as the hairline and down the right side of his face to the mouth. Because of the considerable swelling it was difficult to examine his eyes, but there was no proptosis and the ocular movements were full. The visual acuity of the right eye was reduced (6/24) and that of the left was good (6/4). The conjunctiva was very oedematous but there was no obvious injury, and the anterior segment was otherwise unremarkable. The pupil reactions were normal and fundal examination revealed no abnormality. The left eye was normal.

A provisional diagnosis was made of preseptal cellulitis with septicaemia, and he was admitted to hospital. Swabs from the infected eye were sent for urgent microscopy and culture and blood cultures were taken. The Gram stain revealed Gram-positive cocci. He was then treated with intravenous cefotaxime and gentamicin and topical chloramphenicol and gentamicin drops. Because of the poor visual acuity of the right eye it was thought that an orbital cellulitis could not be excluded despite the normal eye movements and absence of proptosis. He was therefore transferred to the General Hospital under the care of an ear, nose, and throat consultant in order to exclude underlying sinus disease and an associated abscess.

Skull *x*-rays (including sinus views) revealed no abnormality and he was therefore continued on his medical treatment (with the addition of intravenous metronidazole), the presumed diagnosis being preseptal cellulitis. Over the ensuing 12 hours his general condition improved. His temperature fell and his appetite returned. However, the swelling and erythema of the lid and face remained unchanged.

Twenty-one hours after his admission he suffered a

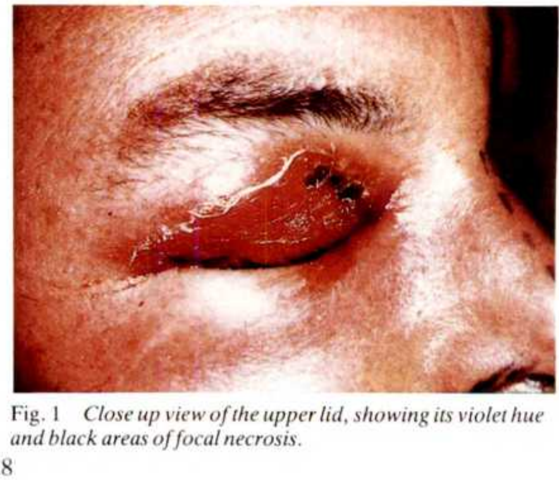

Fig. 1 *Close up view of the upper lid, showing its violet hue and black areas of focal necrosis.*

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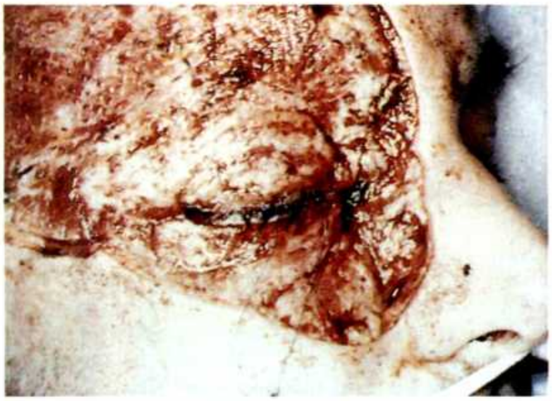

Fig. 2 *Close up view of debrided area around the eye. The lid suture through the upper lid margin enabled the lid to be opened for the application of drops.*

cardiorespiratory arrest and clearly incurred hypoxic brain damage. He was resuscitated and transferred to the Intensive Care Unit. The cause of his arrest at that time remained a mystery in spite of his being intensively investigated. Chest *x*-rays, CT brain scan, and lumbar puncture were normal. Specifically, there was no evidence of intracerebral or intraorbital disease. His temperature rose again, and his white cell count was 22×10^9/l (with a predominant neutrophilia).

By this stage the lid pathology was beginning to reveal its true nature. The lids took on a violet hue and bullae developed. Later, dark areas of focal necrosis appeared (Fig. 1). These features suggested necrotising fasciitis as the true diagnosis as opposed to the initial diagnosis of cellulitis.

Although the original swab grew *Streptococcus viridans* and *Staphylococcus albus*, the original blood culture and a subsequent lid swab yielded β-haemolytic streptococcus (*Streptococcus pyogenes*). All the organisms were sensitive to cefotaxime (this presumably accounted for the resolution of the initial bacteraemia). Benzylpenicillin was added specifically to counter the streptococci. Anaerobic organisms were not isolated. Serological tests revealed a positive anti-DNAse B titre but a negative anti-streptolysin A titre.

As soon as the diagnosis of necrotising fasciitis was made the patient was taken to theatre and extensive areas of his face, lids, and scalp were surgically debrided (Fig. 2). Thereafter the patient's skin condition improved, but the hypoxic brain damage he had incurred during cardiac arrest was sufficient to prevent a recovery of consciousness, and he died 11 days after admission.

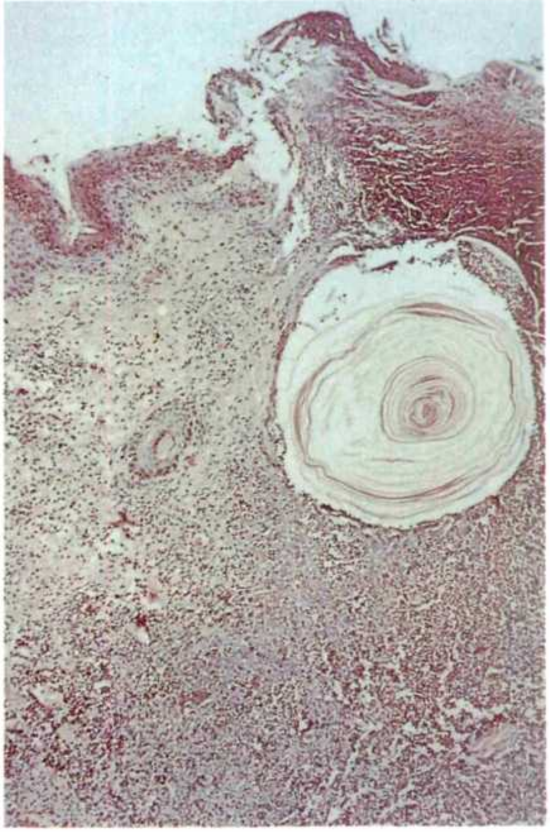

Fig. 3 *Histological section through the excised upper lid tissue, showing the ulcerated skin and acute inflammation extending through the dermis. Haematoxylin and eosin.*

The debrided lid and scalp tissue was sent for histological examination and showed extensive acute inflammatory changes. In the upper lid the epidermis was ulcerated and acute inflammatory changes extended throughout the epidermis and dermis, with thrombus formation in some blood vessels. (Fig. 3). Organisms were not demonstrated despite the use of special stains.

Discussion

Necrotising fasciitis has been recognised as a dangerous and often fatal condition since the American Civil War.[1] However, it was first accurately described as a distinct clinical entity by Meleney in 1924.[2,3] Among its synonyms are streptococcal gangrene, hospital gangrene, gangrenous erysipelas, and necrotising erysipelas. Fournier's gangrene is probably also the same condition.[4] Although originally reported as a relatively rare condition, it is being increasingly recognised that it has probably been underdiagnosed[5,6] in the past and is more common than the numbers of reported cases would at first suggest.

Necrotising fasciitis occurs at all ages, with no statistical difference in race or sex.[7] It is an infection of the skin and subdermal tissue which is most frequently caused by *Streptococcus pyogenes*[1,5,8-11] (group A β-haemolytic streptococcus (BHS)), though *Staphylococcus aureus*[5,7,8,11] and various Gram-negative rods[7,11-13] have also been isolated.

The appearance of necrotising fasciitis may be difficult to diagnose in the early stages. There is often, but not always, a history of injury, usually trivial in nature. In its early stages it is characterised by the acute onset of a painful erythematous rash with associated oedema, which is indistinguishable from cellulitis or early erysipelas. The patient is usually profoundly unwell, with a fever and tachycardia. Within 24–48 hours the tell-tale pathognomonic features develop.[2,3,9] There is a deepening red/violaceous discolouration of the skin with blistering (these bullae can again be confused with erysipelas). Subsequently, black patches of necrosis appear. The affected area may be numb or anaesthetic. The legs are the commonest site for the infection,[5,9] though it can appear anywhere on the body. The area around the eye is not an infrequent site.[14-16]. After four to five days frank cutaneous gangrene develops, which if untreated tends to separate by suppuration by the eighth to tenth day. Lymphangitis and lymphadenopathy are unusual.[9,10,17]

The diagnosis is made principally on the clinical features. However, some investigations are helpful. The white cell count is usually markedly raised (with a neutrophilia). Blood cultures and swabs from the affected site should be taken before antibiotic therapy is instigated. Evidence of streptococcal infection is provided by a raised anti-DNAse B titre in most cases and the anti-hyaluronidase titre may also be raised.[5,18,19] The ASO titre, however, is not usually raised in skin infections[18] and therefore is not helpful in making the diagnosis of necrotising fasciitis.

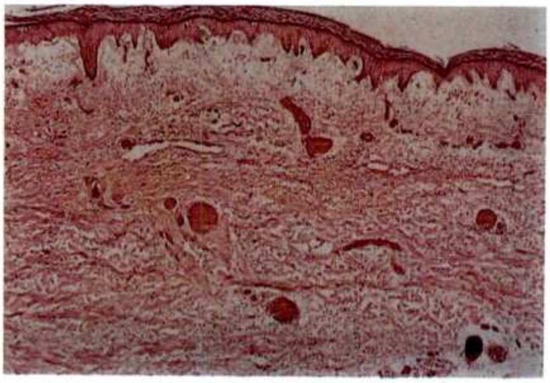

Fig. 4 *Histopathology of necrotising fasciitis demonstrating thrombosis in the blood vessels, in the acutely inflamed dermis. H and E.*

The essential histological feature of the disease is necrosis of the deep fascia and spread of the infection along the fascial planes, with secondary gangrene of the overying skin due to thrombosis of the blood vessels in the subepidermal and subcutaneous tissues[5,10] (Fig. 4). A massive infiltrate of polymorphonuclear leucocytes is present. Antibiotics are unable to reach the necrotic areas, and the bacteria are able to multiply freely. The bacterial toxins can thus have a widespread effect even after the initial septicaemia has been treated. The tissue damage is probably caused by bacterial necrotoxins and thus can also be responsible for some of the pathology remote from the site, which may include glomerulonephritis (resulting in renal failure) and endocarditis.[15]

Initial treatment consists of prompt and intensive intravenous antibiotics. Although the most likely causative pathogen is *Str. pyogenes*, it is wise to cover other possible organisms such as *Staph. aureus* and coliforms. A cephalosporin such as cefuroxime or cefotaxime in high doses is suitable. Penicillin G should be added if streptococci are isolated. Despite adequate antibiotic treatment, patients may still die.[5] Therefore as soon as the diagnosis has been established clinically the affected area should be surgically excised.[2,3,10,14,20-23] This is necessary in spite of the fact that the patient may symptomically improve after treatment with antibiotics.

There is a considerable mortality from necrotising fasciitis (8–50%).[2,8,11,24,25] Although associated illnesses, particularly diabetes mellitis, contribute to this poor prognosis, the principal factors are the time taken to make the diagnosis and delay in surgical intervention.[5,11,26] The decision to debride the infected area is especially difficult when the face is involved because the cosmetic implications are considerable. However, it must be done, and quickly, if increased morbidity and even death are to be avoided.

In summary, necrotising fasciitis is a potentially lethal condition in which speedy investigation, diagnosis, intensive antibiotic treatment, and early surgical debridement is the correct course of management.

I would like to thank Mr Andrew Elkington for his help and advice and for his kindness in allowing me to present this patient, who was under his care. I am grateful also to Dr Barbara Leppard for her advice, to Professor Weller for his help with the histopathology slides, and to Miss Sara Hipwell for preparing this paper for submission.

References

1 Investigations upon the Nature, Causes and Treatment of Hospital Gangrene as it Prevailed in the Confederate Armies 1861–1865, New York, US Sanitary Commission, Surgical Memoirs of the War of Rebellion, 1871. Quoted in Meleney FL. *Treatise on surgical infections*. New York: Oxford University Press, 1948: 15.
2 Meleney FL. Hemolytic streptococcus gangrene. *Arch Surg* 1924; **9:** 317–63.
3 Meleney FL. Differential diagnosis between certain types of infectious gangrene of skin. *Surg Gynecol Obstet* 1933; **56:** 847–67.
4 Cooper DA, Joske RA. Acute streptococcal gangrene of the skin. *Aust NZ J Surg* 1954; **23:** 268–72.
5 Leppard BJ, Seal DV. The value of bacteriology and serology in the diagnosis of necrotising fasciitis. *Br J Dermatol* 1983; **109:** 37–44.
6 Collins RN, Nadel MS. Gangrene due to the haemolytic streptococcus—a rare but treatable disease. *N Engl J Med* 1965; **272:** 578–80.
7 Rea WJ, Wyrich WJ. Necrotising fasciitis. *Ann Surg* 1970; **172:** 957–64.
8 Wilson B. Necrotising fasciitis. *Am Surg* 1952; **18:** 416–31.
9 White WL. Haemolytic streptococcus gangrene. A report of seven cases. *Plast Reconstr Surg* 1953; **11:** 1–14.
10 Strasburg SM, Silver MS. Haemolytic streptococcus gangrene. An uncommon but frequently fatal infection in the antibiotic era. *Am J Surg* 1968; **115:** 763–8.
11 Crosthwait RW Jr, Crosthwait RW, Jordan GL. Necrotising fasciitis. *J Trauma* 1964; **4:** 148–57.
12 Ledingham IMcA, Tehrani MA. Diagnosis, clinical course and treatment of acute dermal gangrene. *Br J Surg* 1975; **62:** 364–72.
13 Fallahzadeh H, Altenbernd E, Mays E. Necrotizing fasciitis. *Am Surg* 1972; **40:** 352–4.
14 Buchanan CS, Haserick JR. Necrotising fasciitis due to group A beta-haemolytic streptococci. *Arch Dermatol* 1970; **101:** 664–8.
15 Seal D, Leppard B, Widdowson J, McGill J, Tormey P. Necrotising fasciitis due to *Streptococcus pyogenes*. *Br Med J* 1980; **282:** 1419–20.
16 Schott EG. Gangrene of the eyelids. *Ind Med Surg* 1966; **29:** 27–9.
17 Hammar H, Wang ERL. Erysipelas and necrotising fasciitis. *Br J Dermatol* 1977; **96:** 409–19.
18 Wannamaker LW. Differences between streptococcal infections of the throat and skin. *N Engl J Med* 1970; **272:** 78–85.
19 Kaplan EL, Wannamaker LW. Suppression of the anti-streptolysin O (ASO) response by lipids extracted from the skin: an explanation or the feeble ASO response following streptococcal pyoderma. *Clin Res* 1973; **21:** 881–6.
20 McCafferty EL Jr, Lyons C. Suppurative fasciitis as the essential feature of haemolytic streptococcus gangrene. With notes on fasciotomy and early wound closure as the treatment of choice. *Surgery* 1948; **24:** 438–42.
21 Meleney FL. Haemolytic streptococcus gangrene. Importance of early diagnosis and early operation. *JAMA* 1929; **92:** 2009–12.
22 Beathard GA, Guckiar JC. Necrotising fasciitis due to group A beta-hemolytic streptococci. *Arch Intern Med* 1967; **120:** 63–7.
23 Le Froch JL, Molavi A. Necrotising skin and sub-cutaneous infections. *J Antimicrob Chemother* 1982; **9** (suppl A): 183–92.
24 Defore WW Jr, Mattok KL, Dang MH, Crawford R, Jordan GL. Necrotising fasciitis: a persistent surgical problem. *J Am Coll Emergency Physicians* 1977; **6:** 62–5.
25 Galosi AF, Herman WP. Fasciitis necroticans. *Dtsch Med Wochenschr* 1979; **104:** 1095–9.
26 Rea WJ, Wyrich WJ. Necrotising fasciitis. *Ann Surg* 1970; **172:** 957–64.

Accepted for publication 23 April 1987.

British Journal of Ophthalmology, 1988, **72**, 432–433

Posterior penetrating injury of the orbit with retained foreign body

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SUMMARY A case of a retained orbital foreign body following a penetrating injury in a 2-year-old boy is described. Diagnosis and management of such cases is discussed.

A 2-year-old boy was referred to the Accident and Emergency Department with a history of having fallen on to the top of a ballpoint pen, cutting his right upper eyelid. The wound had continued to bleed and he had developed a haematoma of the lid. He had become drowsy and vomited on three occasions over a period of two hours.

Examination confirmed that he was drowsy but could be roused. He had a haematoma of his upper eyelid with a 0·7 cm laceration along its medial aspect. His pupils were equal and reactive, ocular movements were full, there was no penetrating injury of the anterior segment of the eye, and no bruits were audible over it. There were no focal neurological signs.

X-ray of the right orbit revealed a foreign body in the posterior part (Figs. 1 and 2). *X*-ray views of the tip of a 'Bic' pen showed this to be identical to the foreign body. A CT scan (Fig. 3) located the foreign body posterior in the orbit lying on the medial wall outside the muscle cone. No intracranial or ocular injury was seen. The child remained neurologically stable.

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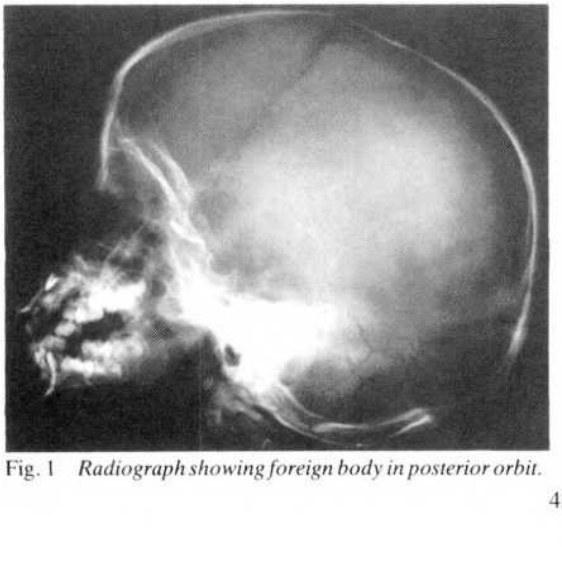

Fig. 1 *Radiograph showing foreign body in posterior orbit.*

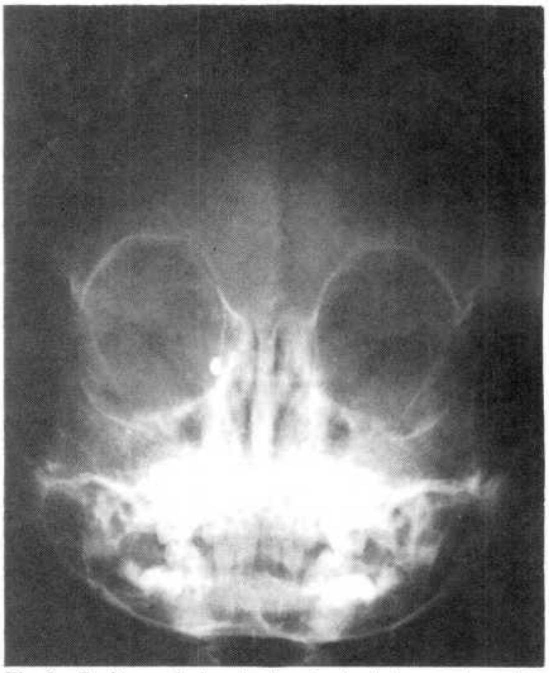

Fig. 2 *Radiograph showing foreign body in posterior orbit.*

Exploration of the right orbit was carried out by subperiosteal approach along the medial wall by an ear, nose, and throat surgeon. The foreign body was located posteriorly in relation to a tear in the

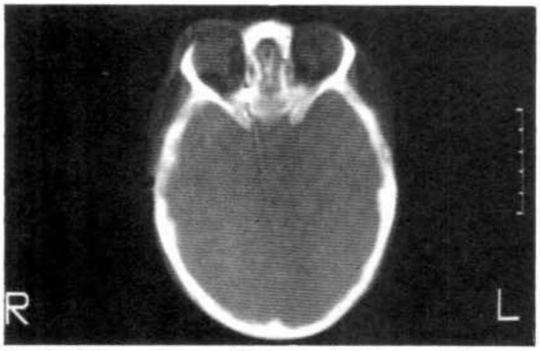

Fig. 3 *CT scan showing foreign body lying on medial orbital wall.*

periosteum and was removed (Fig. 4). Full examination of the globe did not reveal any injury. Oral flucloxacillin was given postoperatively.

The wound settled and the flucloxacillin was stopped. A month after operation a persistent discharge developed from the entry wound which did not respond to oral antibiotics. Swabs of the discharge grew non-haemolytic streptococci. A further exploration of the orbit was undertaken. The pen track was probed, a small amount of pus was found, but there was no evidence of osteitis or further foreign material. The discharge stopped after a further two months on oral Augmentin (potassium clavulanate plus amoxycillin).

Discussion

The case demonstrates the importance of radiography in suspect injuries in children.[1] Once a foreign body is detected, CT scanning is an excellent way of obtaining its precise location.[2] There was no history of a retained fragment from the pen, but the eyelid haematoma and continued bleeding of the wound were suggestive of something more significant.

Cases of deep penetrating foreign bodies entering through the upper inner angle and lying posteriorly in the orbit without injuring the globe have been reported.[3] No cases of the broken off tip of a ballpoint pen have been reported, though a self-inflicted injury caused by driving a ballpoint pen through the wall of the orbit into the intracranial cavity has been noted.[4] Cases of trivial eyelid wounds with intracranial damage have been documented.[5]

Neurological observation to detect a deteriorating conscious level and focal signs is essential in cases where trauma is related to the apex of the orbit, since the injury may involve also the paranasal sinuses and intracranial space.

Inorganic foreign bodies may remain within the orbit for many years without causing signs or symptoms.[3,6] Because of the risk of infection and inflammation in such a vital area it was considered necessary to remove this foreign body. Removal should be undertaken only after carefully locating the foreign body.

A transconjunctival approach is recommended only for anterior orbital foreign bodies. For more posterior foreign bodies adequate access and exposure is possible only by a subperiosteal approach.[7,8]

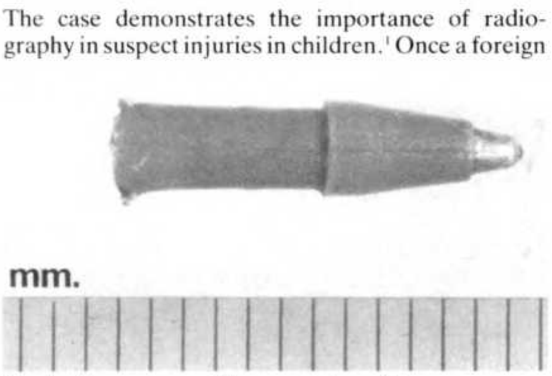

Fig. 4 *Pen tip removed from posterior orbit.*

References

1 Duane TD. *Clinical ophthalmology*. Philadelphia: Harper and Row, 1982; **2:** chapter 22: 23–4.

2 Moseley IF, Sanders MD. *Computerised tomography in neuro-ophthalmology*. London: Chapman and Hall, 1982: 46.

3 Lalla M, Pillai S. Deep penetrating injury of the orbit. *Am J Ophthalmol* 1965; **59:** 922–3.

4 Bowen DI. Self-inflicted orbitocranial injury with a plastic ball-point pen. *Br J Ophthalmol* 1971; **55:** 427–30.

5 Guthkeltch AN. Apparently trivial wounds of the eyelids with intracranial damage. *Br Med J* 1960; ii: 842–4.

6 Peyman GA, Sanders DR, Goldberg MF. *Principles and practice of ophthalmology*. Philadelphia: Saunders, 1980: 2466.

7 Duane TD. *Clinical ophthalmology*. Philadelphia: Harper and Row, 1982; **5:** chapter 14: 7–9.

8 Dudley H, Carter DC, eds. *Rob and Smith's operative surgery, ophthalmic surgery*. 4th ed. London: Butterworths, 1984: 388–93.

Accepted for publication 23 April 1987.

British Journal of Ophthalmology, 1988, **72**, 434–438

Indomethacin retinopathy: case report and review

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SUMMARY The case of a 33-year-old man with probable indomethacin retinopathy is presented. The relevant literature is reviewed and the differences between our case and those previously reported are noted. Our patient appears to have suffered severe and irreversible ocular damage due to the very high dose of indomethacin ingested over a prolonged period.

A 33-year-old man was seen in February 1986. He had noticed a gradual reduction in visual acuity in both eyes for 18 months becoming more noticeable over the past nine months. In addition he gave an 18-month history of difficulty with night vision and increasing photophobia. He had worn glasses since the age of 18 for correction of low myopia (−1·0 D R and L) and reported that in 1978 his optician was unable to improve his right visual acuity to 6/6; an abnormal appearance was noted at the back of that eye. His general health was good, but for eight years up to the age of 25 he took indomethacin 200 mg per day for arthritis of his neck. Subsequently this was taken on an occasional basis for another year, stopping completely in 1979. No other regular medication was taken in conjunction with this and he had never taken chloroquine. There was no family history of eye trouble and no consanguinity.

On examination visual acuity in each eye was 6/24 with glasses but could be improved to 6/18 with the aid of a pinhole. Colour vision was profoundly affected, and he could read only the first of the 17 numbers on the Ishihara plates. The anterior segments were normal, and there were no corneal deposits. There was no relative afferent pupillary defect. The intraocular pressures were normal. There was retinal thinning with pigment mottling, especially in the macular region of both eyes.

Fluorescein angiography confirmed these findings in a rather dramatic fashion and showed a bullseye appearance of the macula (Fig. 1). Electrodiagnostic tests showed a reduced electro-oculogram (EOG) (right 125% and left 140%), and the electroretinogram (ERG) was virtually absent with no oscillatory potential and minimal flicker (Fig. 2).

Visual field assessment with a Goldmann perimeter revealed bilateral central scotomata with constriction to I4 targets (Fig. 3), and a diffuse abnormality in colour vision was demonstrated on the 100-hue test (Fig. 4). A diagnosis of indomethacin retinopathy was made.

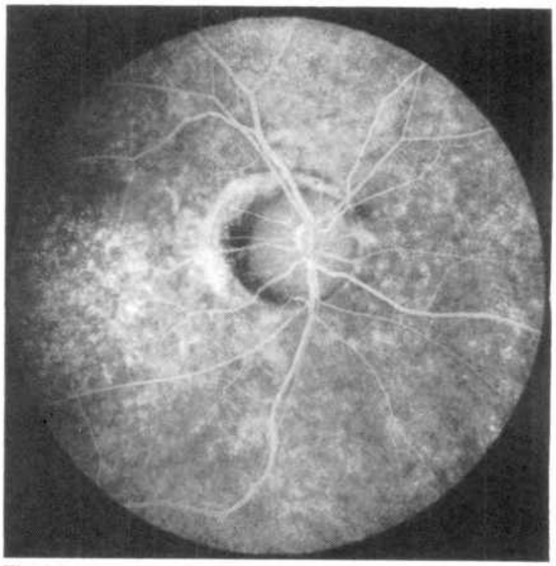

Fig. 1A

Fig. 1 *Fluorescein angiogram of* (A, B) *right optic disc and macula* (C) *left optic disc and macula. There is pigmentary mottling with a bullseye maculopathy.*

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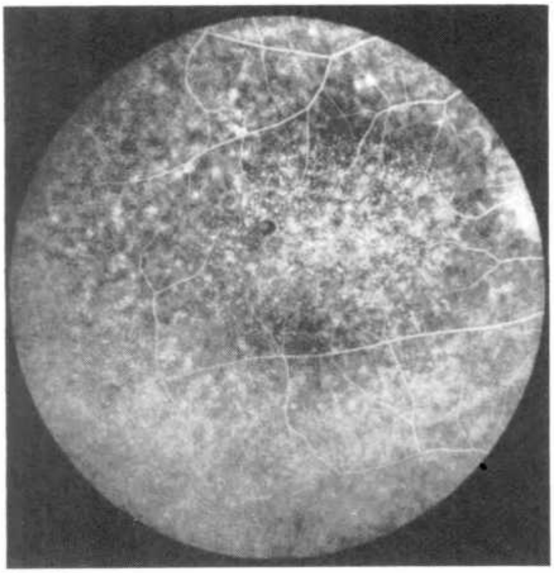


Fig. 1B

Discussion

PREVIOUS REPORTS

Indomethacin, which was first introduced in 1963, is a non-steroidal anti-inflammatory agent which has analgesic and antipyretic properties. It has been used for a wide variety of inflammatory and degenerative joint conditions, acute musculoskeletal disorders, and acute gout.

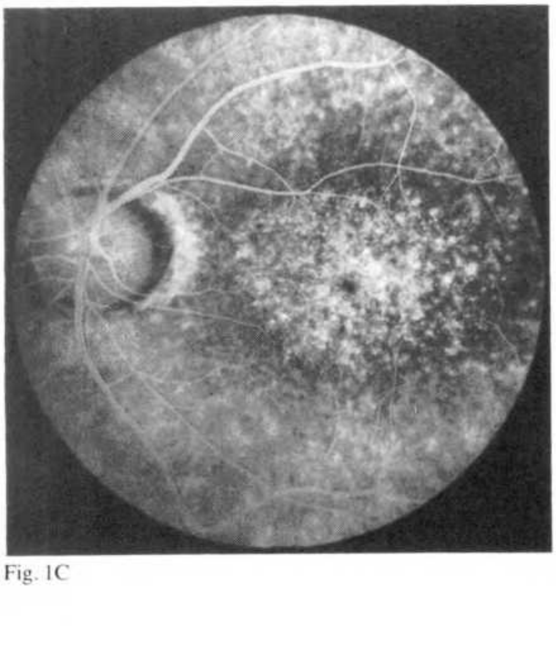


Fig. 1C

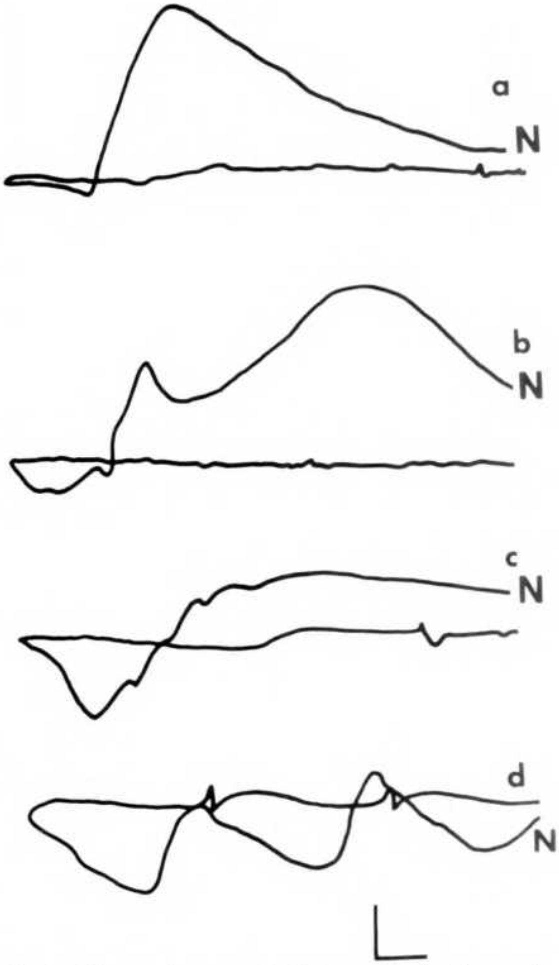


Fig. 2 *Electroretinogram of subject compared with normal* (N): (a) *blue light stimulus,* (b) *red light stimulus,* (c) *white light stimulus,* (d) *response to a 30 Hz flicker. There is an almost absent ERG and minimal flicker. Calibration mark: Gain 100 μV per division for trace* (a), (c), *and* (d) *and 50 μV per division for trace* (b). *Sweep speed scale: 20 ms per division for trace* (a) *and* (b) *and 10 ms per division for trace* (c) *and* (d).

Despite its widespread, frequent, and often prolonged use, ophthalmic side effects seem to be rare. Burns[1] first reported corneal deposits and changes in the retinal pigment epithelium in a 54-year-old man in 1966 and followed this with a series of patients two years later.[2] A further case of retinopathy has been described by Henkes *et al.*,[3] and the ocular side effects in small series of patients have been reported by Carr and Siegel[4] and Palimeris *et al.*[5] Acquired colour vision defects[6,7] and electrodiagnostic changes[8,9] have been reported.

A reduction in visual acuity to 20/70 was reported

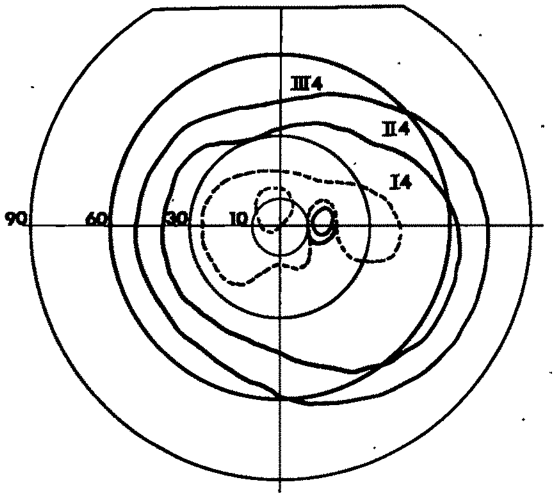


Fig. 3A

Fig. 3 *Goldmann visual fields:* (A) *right eye,* (B) *left eye. There is a bilateral central scotoma and field constriction to I4 targets.*

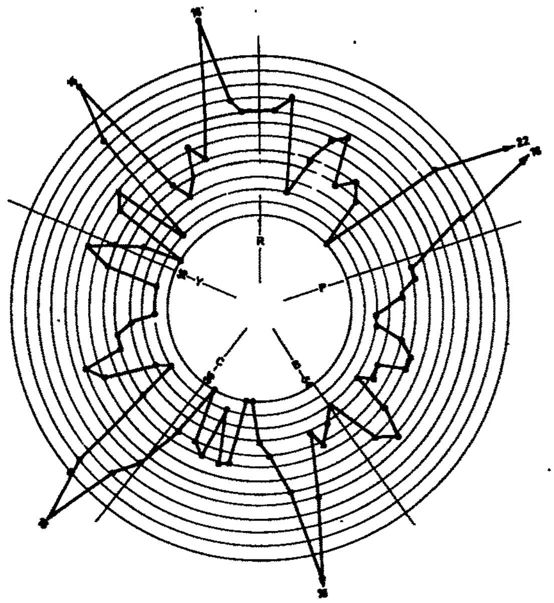


Fig. 4A

Fig. 4 *Farnsworth-Munsell 100-hue test demonstrating a diffuse colour defect,* (A) *right eye,* (B) *left eye.*

by Burns[1] in her original case report, but this returned to 20/20 following withdrawal of treatment. The patient reported by Henkes *et al.*[3] had a worsening of visual acuity on treatment with indomethacin, but there was only a partial recovery off treatment. In the series of 18 patients treated with indomethacin described by Palimeris *et al.*[5] visual acuity was reduced in the three patients noted to have macular changes but normal in the others.

No significant alteration in colour vision was reported by Grützner[6] in a patient who had also received chloroquine, nor in a series of 18 patients receiving indomethacin only, when compared with a control group.[4] Abnormalities have been noted by Burns in one patient, and in that particular case the abormality was unilateral and associated with a central serous detachment. The only reports of

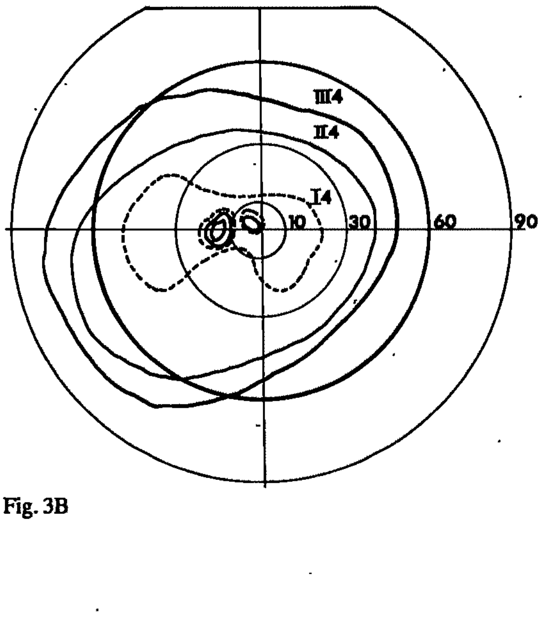


Fig. 3B

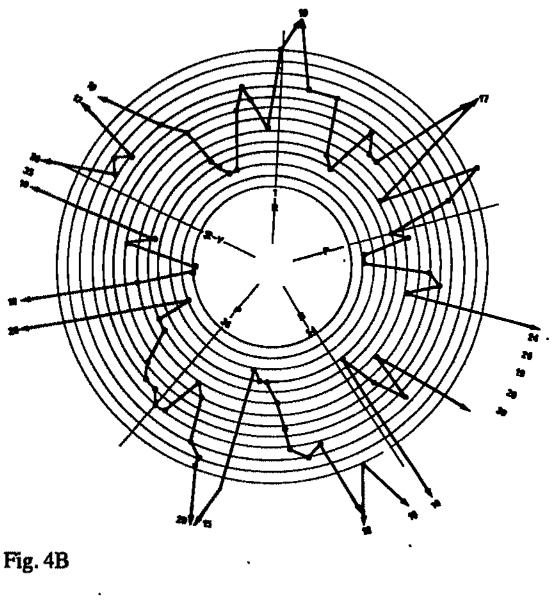


Fig. 4B

definite colour vision changes have come from Palimeris *et al.*,[5] who noted two patients developing acquired defects of the blue-yellow axis after 15 and 17 months of treatment with indomethacin. Both returned to normal after stopping treatment. In a second report from the same department[7] two out of 11 patients were noted to have an acquired blue-yellow defect and one had a diffuse defect of no prominent axis. Again these had returned to almost normal after withdrawal of treatment.

Conflicting reports exist for field changes. Burns described three patients with field constriction and paracentral scotomata with significant improvement following withdrawal of treatment, and similarly, Henkes *et al.*[3] described constriction of field and enlargement of the blind spot during treatment followed by partial recovery. In the two other series no visual field changes nor scotomata were noted,[5] except for one patient with a mild constriction of the visual fields attributed to moderate myopia (−6·0 Dsph R and L).[4]

Macular disturbances were reported in 10 out of 34 cases by Burns.[2] These retinal changes were non-specific and included two cases of macular pucker and a case of central serous retinopathy. The majority, however, were described as having paramacular depigmentation varying in severity from a mottled depigmentation to areas of pigment atrophy. Visual acuity was reduced in all these patients.

It was emphasised that some of these pigmentary changes were very subtle and sometimes best revealed by fluorescein angiography. Carr and Siegel[4] demonstrated no significant ophthalmoscopic changes and no specific features on fluorescein. Palimeris *et al.*[5] noted macular abnormalities in three out of 18 patients. Two of these had perifoveal accumulation of pigment, loss of foveal reflex, and areas of depigmentation round the macula. One case had diffuse perifoveal pigmentation. Although there was some improvement in the ophthalmoscopic picture one year after withdrawal of treatment, the depigmented areas around the maculae remained.

Electrodiagnostic changes have been noted in indomethacin retinopathy. Burns[2] noted a decrease in retinal sensitivity in all cases as shown by a decreased ERG, and Henkes *et al.*[3,9] noted a deterioration of the scotopic ERG and the EOG ratio which improved slowly after withdrawal of treatment to the levels found at the first examination while the patients were taking indomethacin. It was pointed out that this could be interpreted as indicative of a good prognosis, but the visual acuity did not reflect this, and the deep pigmentary changes did not alter significantly. In their study of a selected group of patients who had taken indomethacin for between 12 and 18 months Palimeris *et al.*[5,8] found that indomethacin reduced the amplitude of the ERG in 18% cases, with the scotopic element being more affected than the photopic. The a and b waves of the ERG improved following withdrawal of the drug. In the same group of patients two were found to have an abnormal EOG, with the L/D ratio reduced to 160% in both cases.

One case returned to normal after indomethacin was stopped but the other remained unchanged. They could detect no correlation between ERG and EOG nor could they establish a relationship between dose and signs of toxicity, but they suggested that a total of at least 45 g was needed after one year of treatment. Carr and Siegel[4] could detect no significant difference between their patients and control group of patients, and attributed any abnormalities of the ERG to retinal and choroidal arteriosclerotic changes.

PRESENT CASE

The most striking differences between our patient and the few described in the literature lie in the deterioration in vision several years after withdrawal of indomethacin and the gross changes in the ERG and EOG, which might have been expected to improve. The fluorescein appearance was also particularly striking.

Our patient either has a more severe retinopathy than has previously been reported or a second disease, with indomethacin ingestion being either coincidental or only partly contributory. Chloroquine had never been taken, and we also carefully considered the possibility of cone-rod dystrophy but dismissed it. The macular pigmentary changes were rather more diffuse than usually seen in this condition and more compatible with a toxic retinopathy. In addition there were no significant changes in the peripheral fundus. Although it is impossible to be absolutely certain, we believe that our patient does have an indomethacin retinopathy, with many features qualitatively similar to those described by other authors.

Abnormalities were detected in our patient while he was taking indomethacin, but there was continued deterioration following withdrawal of the treatment. This fact does not, however, exclude indomethacin as a cause of toxicity, since other drugs, notably chloroquine, are known to cause progressive changes long after withdrawal. Indomethacin differs from chloroquine, however, in that it is excreted much more rapidly from the body.

The changes which have been reported elsewhere to be reversible on withdrawal of indomethacin may not be reversible if higher total doses of the drug are ingested. Carr and Siegel,[4] who could demonstrate no retinopathy, looked at patients with a mean dose of 32·8 g, whereas Burns[2 10] in her series looked at patients taking a mean dose of 56·5 g. The patient described by Henkes *et al.*[3] had taken a total dose of 181 g indomethacin in the form of suppositories. The serum concentration, they pointed out, is approximately 50% lower than following the oral ingestion of an equal dose. Our patient, in contrast, had taken over 550 g orally during the eight years of regular use and an additional unknown quantity subsequently when he took indomethacin on a less regular basis.

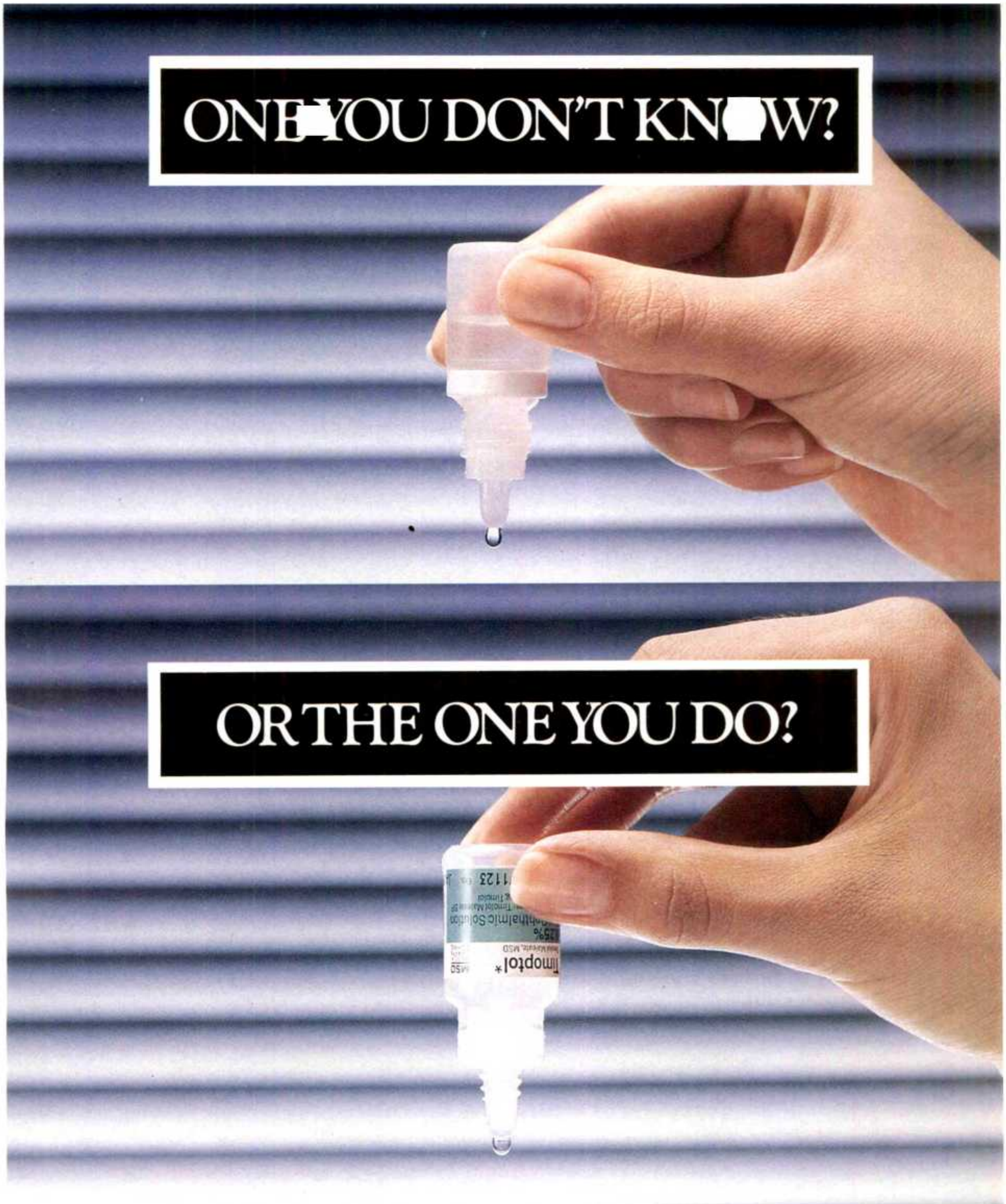
There is a great deal of uncertainty regarding the degree to which indomethacin is retinotoxic. We consider there is sufficient evidence to incriminate it, and it is interesting that both the *British National Formulary* and *MIMS (Monthly Index of Medical Specialities)* state that patients undergoing prolonged therapy should undergo periodic ophthalmic examinations. In clinical practice this is the exception rather than the rule, and further work is needed to evaluate this advice concerning a drug which is widely used.

We are grateful to the staff of the Electrodiagnostic Clinic at Moorfields Eye Hospital for their assistance in recording the electroretinograms and electro-oculograms.

References

1 Burns CA. Ocular effects of indomethacin. Slit lamp and electroretinographic (ERG) study. *Invest Ophthalmol Vis Sci* 1966; 5: 325.
2 Burns CA. Indomethacin, reduced retinal sensitivity and corneal deposits. *Am J Ophthalmol* 1968; **66:** 825–35.
3 Henkes HE, van Lith GHM, Canta LR. Indomethacin retinopathy. *Am J Ophthalmol* 1972; **73:** 846–56.
4 Carr RE, Siegel IM. Retinal function in patients treated with indomethacin. *Am J Ophthalmol* 1973; **75:** 302–6.
5 Palimeris G, Koliopoulos J, Velissaropoulos P. Ocular side effects of indomethacin. *Ophthalmologica* 1972; **164:** 339–53.
6 Grützner P. Acquired colour vision defects secondary to retinal drug toxicity. *Ophthalmologica* 1969; **158:** (suppl): 592–604.
7 Koliopoulos J, Palimeris G. On acquired colour vision disturbances during treatment with ethambutol and indomethacin. *Mod Probl Ophthalmol* 1972; 11: 178–84.
8 Palimeris G, Koliopoulos J, Velissaropoulos P. Electrophysiological findings in patients treated with indomethacin. *Adv Exp Med Biol* 1972; **24:** 323–9.
9 Henkes HE, Deutman AF. Electrodiagnostic procedures in drug induced ocular diseases. *Doc Ophthalmol* 1973; **34:** 209–19.
10 Burns CA. Indomethacin induced ocular toxicity. *Am J Ophthalmol* 1973; **76:** 312–3.

Accepted for publication 23 April 1987.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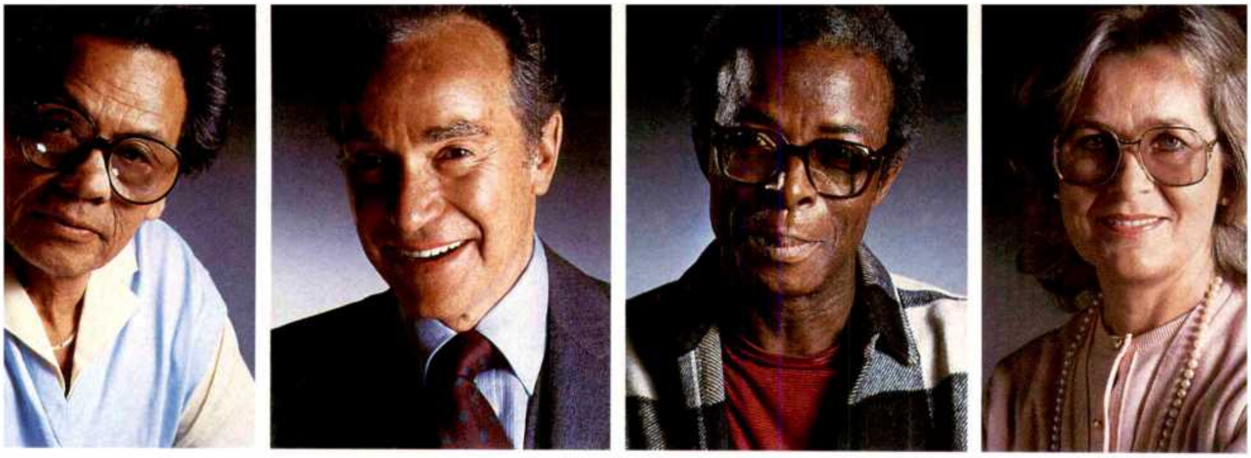

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References

1. Zimmerman, T. J., presented at: Int. Symposium on Glaucoma, XIII Int. Congress o Ophthalmology, Kyoto, Japan, May 1978, 55-64.
2. Sponsel, W. E., *et al., Brit. J. Ophthal.*, 1983, 67, 220-227.
3. Sponsel, W. E., International Symposium on Glaucoma, Turin, 1986.
4. Katz, I. M., presented at: Int. Symposium on Glaucoma, XIII Int. Congress o Ophthalmology, Kyoto, Japan, May 1978, 29.

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Familial grouped pigmentation of the retinal pigment epithelium

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SUMMARY Grouped pigmentation of the retinal pigment epithelium was found in a father and his son. They had a normal resting potential on the electro-oculogram, but the son had a lower normal light rise. We believe this is the first description of familial grouped pigmentation.

Grouped pigmentation of the retinal pigment epithelium has been known for over 100 years,[1] but it was not until 1911 that Höeg[2] used this name to describe clusters of pigment in the retina. The entity has also been called melanosis retinae, bear or animal tracks, and naevoid pigmentation of the fundus. Grouped pigmentation has always been described as being of sporadic nature, though several authors looked for a familial occurrence.[3,4] The only published description of familial grouped pigmentation was by Forgacs and Bozin.[5] Deutman[6] has pointed out that the two sisters described by them possibly did not have grouped pigmentation. In our opinion the description and drawings in their article are more in keeping with naevi that have a slightly hypopigmented border like the halo naevi often found in the skin. Recently we examined a father and son who both had classic grouped pigmentation in their retina.

Case reports

The proband (Fig. 1 case III-3) came to the outpatient department because he had lost his glasses. From age 7 on he was known to have had subnormal visual acuity, attributed to refraction amblyopia. He was healthy and had never taken medicine as a routine.

On examination the visual acuity was right eye 0·5 with +7·5 sph −2·25 axis 15°; left eye 0·8 with +5·5 sph −1·0 axis 170°. The anterior segments and media were clear. In both fundi extensive areas with grouped pigmentation of the retina were visible (Fig. 2). He had central fixation in each eye. Fluorescein angiography revealed blockage of background fluorescence without any leakage on the late phases. The pattern electroretinogram showed normal cone and slightly subnormal rod (RE 80%, LE 70%) responses. The pattern cortical evoked potentials had normal amplitudes and latencies. The electro-oculogram resulted in a light peak-dark trough ratio in the lower normal range (RE 1·76, LE 1·75). The electrophysiological techniques have been described elsewhere.[7] In our set-up the mean light peak-dark trough ratio is 2·20 with a lower limit of 1·60 (2 SD). Kinetic Goldmann perimetry revealed no abnormalities.

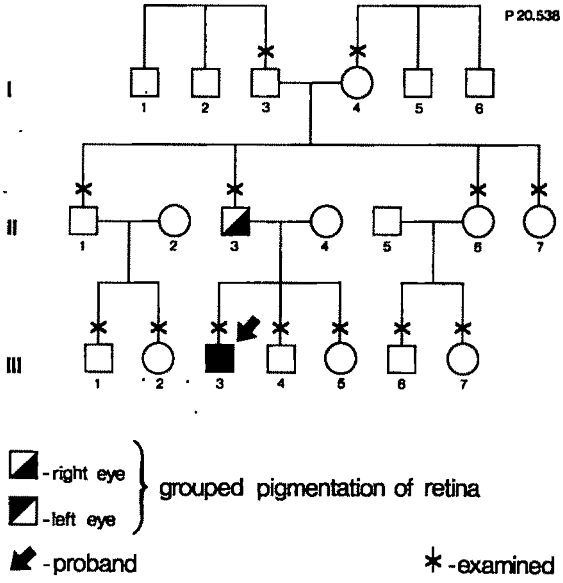

Fig. 1 *Pedigree of family with grouped pigmentation of the retinal pigment epithelium.*

Correspondence to Professor Dr P T V M de Jong, Eye Hospital, Schiedamsevest 180, 3011 BH Rotterdam, The Netherlands.

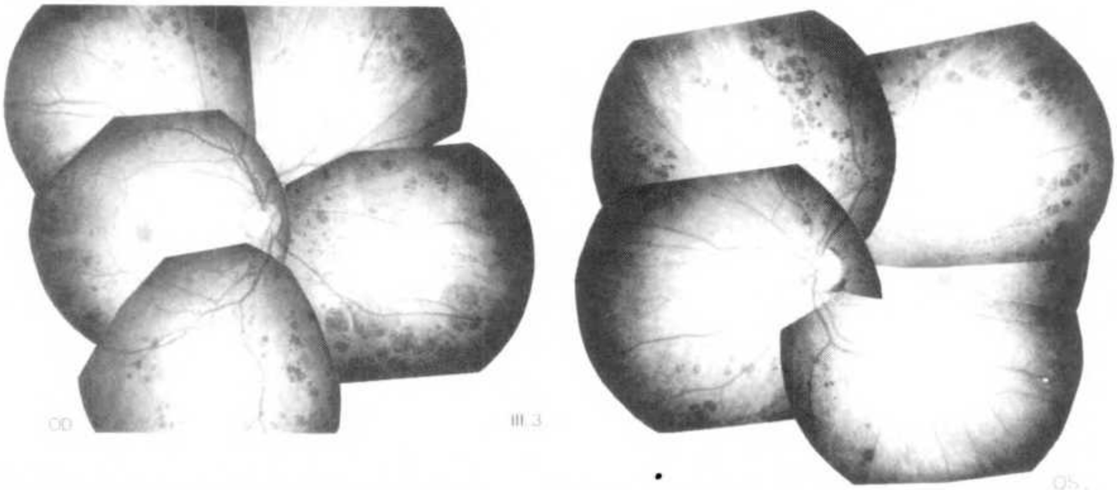

Fig. 2 *Right and left eye of proband, case III-3. Note grouped pigmentations in all quadrants of both eyes.*

His father, case II-3, had no eye complaints but simply accompanied his son to the outpatient department. He consented to allow us to examine his eyes. In both eyes his visual acuity was 1·5 with +0·5 sph. In the right fundus grouped pigmentation of the retinal pigment epithelium was seen in an area inferior to the optic disc (Fig. 3). These lesions were less pigmented than in his son's fundus. The fluorescein angiogram had the same characteristics as his son's. His electro-oculogram gave a normal resting potential and a good light rise (RE 2·29, LE 2·11 light peak-dark trough ratio).

Case III-4 had OU full vision with +0·50 sph. In both eyes discretely pigmented spots were visible at the periphery not clearly resembling grouped pigmentation.

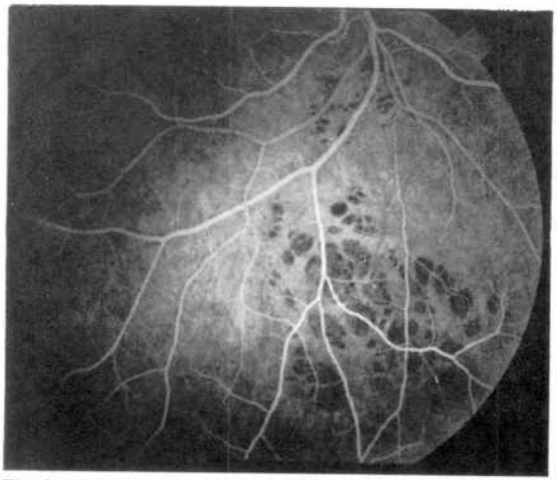

Fig. 3 *Case II-3. Fluorescein angiogram, arteriovenous phase. Grouped pigmentation in area below right optic disc. No leakage on late pictures.*

Case III-5 also had full vision OU and was emmetropic. She had no pigmentary anomalies.

It was not possible for the other family members, some living abroad, to be examined by the authors. They all had a dilated fundus examination by their own ophthalmologists, who were specifically asked by the authors to look for grouped pigmentations. None of them had grouped pigmentation or hypermetropia greater than +0·75.

Discussion

We believe this to be the first report of familial occurrence of unquestionable grouped pigmentation of the retinal pigment epithelium. The exact prevalence of this benign abnormality is unknown. The Framingham eye study[8] did not specifically look for all kinds of fundus abnormalities. The investigator, however, while looking for macular degeneration, was required to record pigment disturbances in the macula, the perimacular area, or of unknown location in the eyes with visual acuity 20/30 or worse. In 5253 eyes no mention of grouped pigmentation was made. We found only one report[9] in which it was stated that three cases were seen in an examination of 2500 eyes without any further epidemiological data. If it is assumed that the reasons for seeing an ophthalmologist were the same in 1891 as in 1986 and that the prevalence of grouped pigmentation has remained constant, we could calculate that the prevalence nowadays would be 0·12% in an ophthalmic population. The chances that both a father and his son would have grouped pigmentation by coincidence would be smaller than 1:1 000 000, because the father was not an ophthalmic patient but simply an accompanying person. It thus seems likely that grouped pigmentation is a disorder of autosomal dominant inheritance with variable expression.

This might place grouped pigmentation among the pattern dystrophies as a hereditary disorder of the retinal pigment epithelium with a normal or slightly subnormal visual acuity, blockage of background fluorescence on the angiogram with no leakage on the late phases, and an electro-oculogram in the lower normal range. So far as we know what constitutes a pattern dystrophy has never been exactly defined. Some people claim that a bilateral, symmetrical, progressive disorder should be present, but in many cases described as pattern dystrophy these conditions were not met.

The subnormal visual acuity of our proband may possibly be attributed to his hypermetropic astigmatism resulting in amblyopia. From an early age he was known to have subnormal visual acuity. We think it unlikely that this acuity was affected by the grouped pigmentation, as he had no abnormal pigmentation in his macula and we found a report stating that the photoreceptors overlying the pigmented areas in grouped pigmentation showed only post mortem changes.[10] On the other hand hypermetropia has previously been mentioned in relation to grouped pigmentation.[4]

It has been suggested that grouped pigmentation and congenital hypertrophy of the retinal pigment epithelium are different expressions of the same disorder.[11 12] We disagree because of the difference in morphology and, because in contrast to the cases with grouped pigmentation, the congenital hypertrophy cases showed lack of photoreceptors above the lesions,[13] abnormal visual fields,[11 13] reported growth,[14] and abnormal vessels above the hypertrophy.[15] Congenital hypertrophy of the retinal pigment epithelium, however, has also been shown to be hereditary in cases of Gardner's syndrome[16] and in one family with microcephaly and hyperreflexia.[17]

This family had no history of hereditary abnormalities. Grouped pigmentation has been associated with convergent squint,[2] macular coloboma,[18] and chondrodysplasia,[19] but in the last case we think the description fits more that of pigment epithelial hypertrophy. We have personally seen a case of Rieger's anomaly and grouped pigmentation.[20] Most patients with grouped pigmentation have no eye complaints, so that the pigmentation will often be a coincidental finding. It seems likely that systemic examination of sibships would disclose more familial cases of grouped pigmentation of the retinal pigment epithelium.

References

1 Mauthner L. *Lehrbuch der Ophthalmoscopie.* Wien: Tendler, 1868.
2 Höeg N. Die gruppierte Pigmentation des Augengrundes. *Klin Monatsbl Augenheilkd* 1911; **49:** 49–77.
3 Tower P. Congenital grouped pigmentation of the retina. *Arch Ophthalmol* 1948; **39:** 536–41.
4 Meunier A, Boursin P. La pigmentation groupée de la rétine. *Bull Soc Belge Ophtalmol* 1951; **99:** 470–8.
5 Forgacs J, Bozin I. Manifestation familiale de pigmentations groupées de la région maculaire. *Ophthalmologica* 1966; **152:** 364–8.
6 Deutman AF. In: Krill AE, ed. *Hereditary retinal and choroidal diseases.* Hagerstown: Harper and Row, 1977: **2:** 730–6.
7 Arden GB, Barrada A, Kelsey JH. New clinical tests of retinal function based upon the standing potential of the eye. *Br J Ophthalmol* 1962; **46:** 449–67.
8 Framingham Eye Study. *Surv Ophthalmol* 1980; **24** (suppl): 435.
9 Stephenson S. A peculiar form of retinal pigmentation. *Trans Ophthalmol Soc UK* 1891; **11:** 77–82.
10 Shields JA, Tso MOM. Congenital grouped pigmentation of the retina. Histopathologic description and report of a case. *Arch Ophthalmol* 1975; **93:** 1153–5.
11 Purcell JJ, Shields JA. Hypertrophy with hyperpigmentation of the retinal pigment epithelium. *Arch Ophthalmol* 1975; **93:** 1122–6.
12 Feys J, Salvanet-Bouccara A. Hypertrophies de l'épithelium pigmentaire. *J Fr Ophtalmol* 1981; **4:** 117–21.
13 Buettner H. Congenital hypertrophy of the retinal pigment epithelium. *Am J Ophthalmol* 1975; **79:** 177–89.
14 Norris JL, Cleasby GW. An unusual case of congenital hypertrophy of the retinal pigment epithelium. *Arch Ophthalmol* 1976; **94:** 1910–1.
15 Cleary PE, Gregor Z, Bird AC. Retinal vascular changes in congenital hypertrophy of the retinal pigment epithelium. *Br J Ophthalmol* 1976; **60:** 499–503.
16 Blair NP, Trempe CL. Hypertrophy of the retinal pigment epithelium associated with Gardner's syndrome. *Am J Ophthalmol* 1980; **90:** 661–7.
17 Parke JT, Riccardi VM, Lewis RA, Ferrell RE. A syndrome of microcephaly and retinal pigmentary abnormalities without mental retardation in a family with coincidental autosomal dominant hyperreflexia. *Am J Med Genet* 1984; **17:** 585–94.
18 McGregor IS. Macular coloboma with bilateral grouped pigmentation of the retina. *Br J Ophthalmol* 1945; **39:** 132–6.
19 Collier M. Les manifestations oculaires associées à la dyschondroplasie d'Ollier. *Bull Soc Ophthalmol Fr* 1961; **4:** 161–9.
20 de Jong PTVM, Delleman JW, Witmer JP, Zeilstra C. Rieger's anomaly with retinal pigmentations. *Ophthalmologica* 1979; **178:** 107–8.

Accepted for publication 14 April 1987.

British Journal of Ophthalmology, 1988, 72, 442–447

A longitudinal study of clinical and immunological findings in 52 patients with relapsing retinal vasculitis

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SUMMARY Fifty-two patients with retinal vasculitis—26 with idiopathic disease and 26 with associated systemic inflammatory disease—were followed up for periods ranging from six months to 12 years. The aim of the study was to determine the relationship between relapse of uveitis, visual outcome, and the occurrence of circulating immune complexes (CIC) and antiretinal antibodies. In a total of 69 relapses, CIC were increased in one-third of patients and antiretinal antibodies in one-half. In those 34 patients who expressed antiretinal antibodies 27 (79%) of the relapses were characterised by antiretinal antibodies in the absence of raised CIC levels ($p<0.01$). These findings support our previous hypothesis that CIC may have a protective role in autoimmune retinal vasculitis and that antiretinal autoimmunity is of pathogenetic importance in relapse. In individual patients the visual outcome was not related to the number of relapses or to the CIC-autoantibody pattern, suggesting the operation of additional features which merit identification.

Retinal vasculitis is a significant cause of blindness in young people. Clinical diagnosis depends on evidence of inflammation within the eye (for example, cells in the vitreous), together with involvement of the retinal vessels (for example, periphlebitis, vascular occlusion, or fluorescein leakage). The main causes of visual loss are macular oedema and retinal vascular occlusion occasionally leading to neovascularisation and vitreous haemorrhage. Retinal vasculitis may be either idiopathic or associated with systemic inflammatory disease (for example, sarcoidosis, Behçet's disease). Both cell mediated and humoral immunity to specific retinal antigens together with raised circulating immune complex levels have been demonstrated in patients with retinal vasculitis of varying aetiologies. In a recent point-prevalence study[1] we showed that 70% of all patients with retinal vasculitis expressed retinal autoimmunity, and that in patients with severe idiopathic retinal vasculitis there was an inverse relationship between pronounced antiretinal antibody levels and the occurrence of raised circulating immune complexes.

We present the results of a longitudinal study of 52 patients with relapsing retinal vasculitis which was carried out to see if these immunological markers could also predict the course and outcome of disease.

Materials and methods

Fifty-two patients were recruited into the study from those attending the Medical Eye Unit at St Thomas's Hospital. The majority of these patients had been diagnosed elsewhere and referred for assessment, the rest being admitted from the Casualty Department. In all cases the diagnosis was confirmed by the clinical and fluorescein angiographic appearances. The patients had all been followed up regularly (2–3 month assessments) for a minimum of six months. Twenty-six patients had retinal vasculitis alone (RV), and 26 had retinal vasculitis in association with systemic inflammatory disease (RV+SID). In the latter group 22 patients had Behçet's disease, three had sarcoidosis, and one had juvenile polyarthritis. Patients with infective or malignant disease, or whose follow-up was less than six months, were excluded from the study. Previous treatment was not a contraindication to inclusion.

A full ophthalmological assessment was carried

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out at each hospital visit and included tests of best corrected visual acuity, near vision, colour vision, slit-lamp examination, and indirect ophthalmoscopy. At most of his attendances the patient was seen by one ophthalmologist (EG). Fluorescein angiography was performed whenever clinically indicated. Disease severity was scored on a 20-point system in which specific ophthalmological features were weighted according to the considered impact on short-term visual morbidity.[1]

The course of the disease was described in terms of the number of relapses for each patient. A relapse was defined as an increase in visual symptoms (blurred vision, floaters) associated with an increase in vitreous cellularity. This was often associated with the appearance of one or more new features of retinal inflammation (macular oedema, retinal infiltrates, vascular occlusion). An individual relapse was frequently, though not always, associated with an increase in the disease severity score and with a reduction in visual acuity.

The outcome of disease was described in terms of overall changes in visual acuity during the study period. For the purposes of this study corrected visual acuity was graded as follows: 'excellent' (grade I: 6/6 or better); 'good' (grade II: 6/9 or 6/12); 'fair' (grade III: 6/18 to 6/36); and bad (grade IV: 6/60 or worse). A good visual outcome was defined as either (*a*) maintenance of a visual acuity of 6/12 or better; or (*b*) improvement of one or more grades by the end of the study period. Patients who did not fulfil either of these criteria were considered to have had a poor visual outcome.

Patients were treated with combinations of topical therapy (steroids, mydriatics), systemic corticosteroids, and immunosuppressives (for example, azathioprine, chlorambucil, colchicine, and cyclosporin A). In general, patients with a visual acuity of less than 6/12 were treated systemically at a starting dose of prednisolone 60 mg/day, with an immunosuppressive agent being added after six weeks if the disease did not remit.

Blood was taken from all patients at each visit for immunological assessment.

IMMUNOLOGICAL ASSESSMENT

Circulating immune complex (CIC) measurements and complement screening tests

CIC were measured by two methods: (*a*) Serum was precipitated with 2% polyethylene glycol (PEG), and the IgG content of the precipitate was measured by radial immunodiffusion. (*b*) Serum was reacted with solid phase human C1q. Immune complexes were then determined by reactivity with a ^{125}I-labelled antiglobulin reagent, the test being calibrated with aggregated human IgG. The sensitivity of the method was increased by preincubating C1q-coated tubes with non-labelled rabbit IgG antibody directed against the Fc fragment of human IgG. This method reduced the prevalence of false negative results in sera containing rheumatoid factor.

Complement screening tests were done on all sera, with haemolytic plates for testing the functional activity of classic and alternative pathways and radial immunodiffusion for measuring components C3 and C4. CIC levels were considered to be raised when C1q or PEG results were more than 2 SD above the normal mean (for C1q:14·2±1·2 mg/l equivalent aggregated IgG; for PEG: >4·9 g/l equivalent IgG). An abnormal complement screen was recorded when the result of any of the four tests fell outside the normal range.

Retinal specific autoantibodies

Antiretinal antibodies were measured by two methods: (*a*) Passive haemagglutination of sheep erythrocytes to which bovine S antigen had been coupled with the aid of chromium chloride. (*b*) Indirect immunofluorescent staining of frozen sections of human retina. The specificity of antiretinal immunofluorescence was established by the use of a reference standard guinea-pig antiserum, raised against photoreceptor antigen, which did not contain antinuclear antibodies or antibodies to smooth muscle. Retinal autoantibodies were considered to be present if fluorescence was found in the photoreceptor layers of cones and rods and the cytoplasm of the outer nuclear and outer plexiform layers. As sera from healthy controls occasionally gave antiretinal immunofluorescence at 1:5 dilution, or a passive haemagglutination titre of 1:16, positive results were recorded when antibodies were detected at titres of >1:10 by immunofluorescence or >1:32 by haemagglutination.

Statistical analysis. All results in this study were analysed by χ^2 test.

Results

Fifty-two patients who had been followed up for six months or more were included in this study—26 patients with RV alone and 26 with RV+SID.

Patients in the RV group were 13 to 70 years old (mean 37 years), attended for six to 56 months (mean 25 months), and had immunological assessments on two to 14 occasions (mean seven). Patients in the RV+SID group were 19 to 63 years old (mean 36), attended for six to 45 months (mean 18 months), and had immunological assessments on two to 25 occasions (mean nine). In all, individual ophthalmological and immunological assessments were made in these patients on 449 occasions.

Table 1 *Incidence of relapse in 52 patients with retinal vasculitis*

	RV *(26 patients)*	*RV+SID* *(26 patients)*
0 relapse	6	3
1 relapse	8	12
2 relapses	10	10
3 relapses	2	1
Total no. of relapses	34	35

Table 2 *Immunological findings during 69 relapses in all 52 patients*

	Ret AB+	*Ret AB−*
CIC+	7 (10%)	16 (23%)
CIC−	27 (39%)	19 (28%)
Total	34	35

χ^2 test, $p=>0{\cdot}05$.

RELAPSES

The number of relapses for each patient in both groups is shown in Table 1. The 26 patients in the RV group had a total of 34 relapses and the 26 patients in the RV+SID group had 35 relapses. At the time of relapse the CIC concentrations were raised in 38% of patients with RV and 31% of patients with RV+SID, and antiretinal antibodies were found in 68% of patients with RV and 66% of patients with RV+SID. These features alone did not distinguish the two groups of patients. When both tests were examined together (Table 2), 28% of patients showed neither raised CIC nor retinal autoantibodies; one-third did have high CIC but associated with retinal antibodies in only 10%. In contrast, 39% of patients who did not have high CIC did express retinal autoimmunity ($p>0{\cdot}05$).

The relationship between CIC and retinal autoantibodies during relapse, which excludes patients not expressing immunological abnormalities, is shown in Table 3. In patients with RV five relapses (32%) occurred when both CIC and retinal antibodies were present, but 11 (58%) relapses occurred when retinal antibodies were present alone. Similarly in patients with RV+SID only two (9%) relapses occurred when raised CIC and retinal autoantibodies were present, but 16 (91%) with retinal autoantibodies alone ($p<0{\cdot}001$). In RV 10 (29%) relapses occurred in the absence of immunological abnormality and nine (26%) in RV+SID.

Table 3 *Relationship between CIC and retinal autoimmunity during relapses in patients expressing immunological abnormalities*

	CIC positive		*Ret. ab. positive*	
	Ret. ab. positive	*Ret. ab. negative*	*CIC positive*	*CIC negative*
RV	5	8	5	11
RV+SID	2	8	2	16
Total	7	16	7	27

Ret. ab.=retinal antibodies. CIC positive by either C1q or polyethylene glycol. Ret. ab. positive by either passive haemagglutination or indirect immunofluorescence tests. χ^2 test, $p<0{\cdot}001$.

Table 4 *Immunological changes during quiescent disease*

	RV	*RV+SID*
Ret. Ab. +	82 (48%)	64 (30%)
−	87 (52%)	147 (70%)
CIC+	48 (28%)	54 (25%)
−	121 (72%)	157 (75%)

Ret. ab.=retinal antibodies.

Table 5 *RV+SID: Retinal autoantibodies and disease activity*

	Quiescent	*Active*	
Ret. ab. +	64	26	90
Ret. ab. −	147	9	156
Total	211	35	246

χ^2 test, $p\leq0{\cdot}001$

This table confirms that patients with RV+SID were much more likely to show retinal autoimmunity during active phases of disease. (There was not any similar correlation when CIC levels were considered in relation to disease activity.)

There was no correlation between CIC levels and the number of relapses. In RV 6% of patients with two or more relapses and 7% of patients with one or no relapses had raised CIC. The figures for RV+SID were 8% and 9% respectively.

Patients were assessed clinically and immunologically 380 times when their disease was judged to be quiescent (RV, 169; RV+SID, 211: Table 4). At these inactive times CIC concentrations were raised in 28% of patients with RV and 25% of patients with RV+SID and retinal autoantibodies in 48% of RV patients and 30% of RV+SID patients. In RV+SID retinal antibodies were significantly more prevalent in patients at the time of relapse (Table 5, $p<0{\cdot}001$). There was no similar correlation in RV, and the presence of CIC did not distinguish the two phases of disease in either group. Complement screening did not show any abnormality in the two groups of patients.

Relapses were often associated with development of periphlebitis, vascular occlusion, macular oedema, or retinal infiltrates. Patients presented with periphlebitis on 60 occasions, which tended to occur with a rise in retinal autoantibodies. However, when patients presented with macular oedema, retinal autoimmunity was not usually expressed.

Table 6 *Relationship between visual outcome and relapse rate*

	Good visual outcome	*Poor visual outcome*
RV		
High relapse rate	7	5
Low relapse rate	5	9
Total	12	14
RV+SID		
High relapse rate	6	5
Low relapse rate	4	11
Total	10	16

VISUAL OUTCOME

Twelve patients with RV had a good visual outcome and 14 patients had a bad visual outcome. Similarly in RV+SID 10 patients had a good visual outcome and 16 a bad visual outcome.

There was no correlation between the number of relapses and the visual outcome in either group, though all three patients with three relapses had a bad visual outcome (Table 6).

In patients with RV the CIC concentrations were raised in 29% of patients with a good visual outcome and 27% patients with a bad visual outcome; retinal autoantibodies occurred in 48% of patients with good visual outcome and 52% patients with bad outcome.

In patients with RV+SID 20% of patients with a good visual outcome had raised CIC concentrations and 29% patients with a bad visual outcome; 43% of patients with a good outcome and 33% of patients with a bad outcome showed retinal autoimmunity. Hence these abnormalities did not distinguish between a good or bad visual prognosis in either group of patients. When the number of relapses, visual outcome, and immunological status were examined together, no significant features were found to distinguish patients in any group.

Figs. 1 and 2 illustrate the recording of clinical and immunological progress of two patients with RV. Patient 1, with a bad outcome, showed frequent retinal autoantibodies, particularly during relapses (high disease score) but generally not in association with raised CIC. Patient 2, with a good outcome, often had raised CIC during relapses, sometimes together with retinal antibodies, but did not express retinal autoimmunity in the absence of raised CIC.

TREATMENT

Twenty patients with RV required systemic treatment, and only six did not require any systemic or immunosuppressive treatment throughout the follow-up period. Only one patient with RV+SID did not require systemic treatment, all the remaining 25 requiring both steroids and immunosuppressives. Systemic treatment reduced the disease activity in all patients, but it was impossible to evaluate the effect of systemic therapy on immunological features because only three patients changed their mode of treatment during the follow-up period.

Discussion

The present study was undertaken to identify patterns of immunological behaviour that might predict visual prognosis in patients with relapsing retinal vasculitis. The study revealed that disease relapse is frequently associated with antiretinal antibodies unaccompanied by raised CIC levels. In idiopathic RV raised CIC levels did not distinguish an active phase from a quiescent phase of the disease. However, further examination of the patients with RV accompanying Behçet's disease showed that, although the level of antiretinal antibodies did not fluctuate during the course of retinal disease, raised CIC levels tended to occur just before or just after the

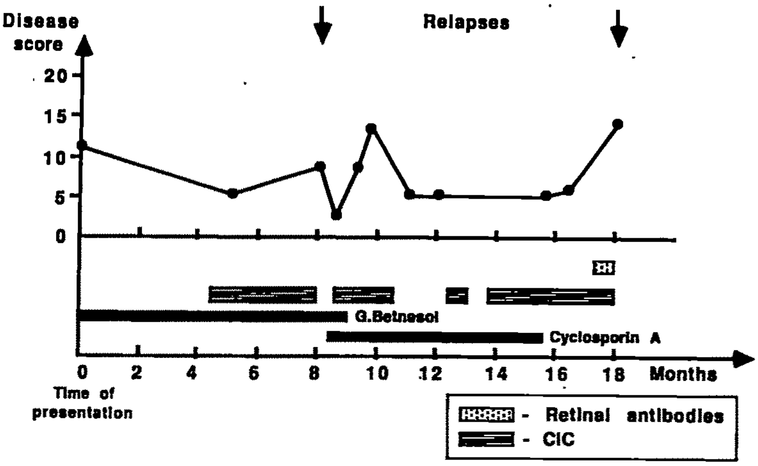

Fig. 1 *Flow chart showing the clinical and immunological progress of a patient with retinal vasculitis and a bad visual prognosis. Antiretinal autoantibodies are raised prior to a relapse (arrows) in the absence of circulating immune complexes. G. Betnesol=betamethasone eyedrops.*

period of relapse. A similar observation was made by Nussenblatt *et al.* in patients receiving cyclosporin A for their Behçet's disease.[2] On occasion raised CIC levels occurred during relapses in the absence of retinal autoimmunity; this suggests an immune complex mediated pathogenesis and was particularly observed in patients with Behçet's disease.

Our study did not show any correlation in either RV or RV+SID between relapse rate and visual prognosis, or between CIC, retinal autoimmunity, and visual prognosis.

The longitudinal relationship of CIC levels and retinal autoimmunity in posterior uveitis has been examined in three previous reports.[3-5] Abrahams and Gregerson reported that there was no correlation between clinical activity and titres of antibody to S antigen in four patients with relapses—three with idiopathic disease and one with sarcoidosis.[4] In a further study[3] it was reported that patients with only one attack of uveitis showed a gradual decrease in antiretinal antibody titres after the acute attack, while in patients with recurrent attacks of uveitis antiretinal antibody levels were generally stable. We could not confirm this observation in patients with RV+SID, though there was a trend towards it in patients with RV alone. Heckenlively *et al.* studied patients with non-inflammatory retinal disease and showed a significant correlation between antiretinal antibodies and various features on fluorescein angiography such as macular odema and disc staining.[5]

Antibodies to S antigen rise after argon laser therapy for diabetic retinopathy, which suggests that retinal destruction initiates an immune response and consequent antibody formation.[6] This might lead one to expect an increase in antibody titres during the course of a disease such as Behçet's when relentless retinal damage occurs secondary to consecutive venous occlusions. However, we did not observe such a change in antibody titre. Retinal antibodies were measured in this study by both passive haemagglutination and indirect immunofluorescence. In both tests the autoantigens are not fully specified: thus indirect immunofluorescence is undertaken with frozen sections of human retina that contain several potential autoantigens (S antigen, rhodopsin, interphotoreceptor binding protein). This heterogeneity of autoantigens may underlie the lack of correlation between disease severity and antibody levels in our study; related findings have been observed in other organ specific diseases such as myasthenia gravis.[7]

Immunological findings were not altered by changes in systemic therapy. The majority of patients were not taking systemic steroids when first examined, and we were unable to substantiate the findings of Gregerson *et al.*[8] that systemic therapy reduces the levels of antibodies.

There is substantial evidence that retinal vasculitis is an immunologically mediated disease. The ocular inflammation often accompanies a systemic inflammatory disease of known immunological background, such as sarcoidosis and Behçet's disease.[9 10] Sera from patients with retinal vasculitis may contain circulating immune complexes,[11] or antibodies to retinal S antigen,[1] and their lymphocytes may show abnormal T cell responses to both standard mitogens and S antigen.[12] Despite this knowledge the pathogenesis of retinal vasculitis in any given patient remains elusive. However, this study lends support to our view that in isolated retinal vasculitis antiretinal

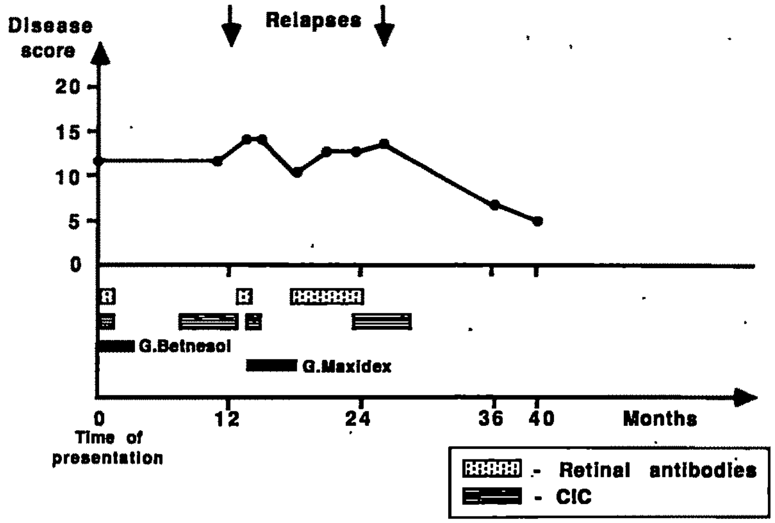

Fig. 2 *Flow chart showing the clinical and immunological features of a retinal vasculitis patient with a good visual prognosis. The first relapse (arrows) is preceded by a rise in antiretinal antibody titre and its recovery with the development of CIC. A further attack is again associated with a raised antiretinal antibody titre in the absence of CIC. G. Betnesol=betamethasone eyedrops. G. Maxidex=dexamethasone+hypromellose eyedrops.*

autoimmunity is pathogenic and that CIC may have a compensatory or protective role.[13] In patients with RV+SID it appears that CIC may play a part in disease pathogenesis along with antiretinal antibodies in some patients.

We are indebted to Mr Richard Dewhirst for the illustrations and Miss Josephine Lace for secretarial assistance. This work was supported by grants from the Medical Research Council (Grant No. G.8303319 SB), the TFC Frost Charitable Trust, Research (Endowments) Committee, St Thomas's Hospital, the Frances and Augustus Newman Foundation, and the Iris Fund for Prevention of Blindness. Mr M R Stanford holds an MRC Training Award Fellowship.

References

1 Dumonde DC, Kasp Grochowska E, Graham E, *et al.* Antiretinal autoimmunity and circulating immune complexes in patients with retinal vasculitis. *Lancet* 1982; ii: 787–92.

2 Nussenblatt RB, Palestine AG, Chan C, Mochizuki M, Yancy K. Effectiveness of cyclosporin therapy for Behçet's disease. *Arthitis Rheum* 1985; **28**: 671–9.

3 Abrahams IW, Gregerson DS. Longitudinal study of serum antibody responses to retinal antigens in acute ocular toxoplasmosis. *Am J Ophthalmol* 1982; **93**: 224–31.

4 Abrahams IW, Gregerson DS. Longitudinal study of serum antibody responses to bovine retinal S antigen in endogenous granulomatous uveitis. *Br J Ophthalmol* 1983; **67**: 681–4.

5 Heckenlively JR, Solish AM, Chant SM, Meyers-Elliott RH. Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings. *Br J Ophthalmol* 1985; **69**: 758–64.

6 Gregerson DS, Abrahams WI, Puklin JE. Serum antibody responses to bovine retinal S antigen and rod outer segments in proliferative diabetic retinopathy before and after argon laser photocoagulation. *Ophthalmology* 1982; **89**: 767–71.

7 Roses AD, Alonow CW, McAdams MW, Lane RJM. No direct correlation between serum antiacetylcholine receptor antibody levels and clinical state of individual patients with myasthenia gravis. *Neurology* 1981; **31**: 220–4.

8 Gregerson DS, Abrahams IW, Thirkill CE. Serum antibody levels of uveitis patients to bovine retinal antigens. *Invest Ophthalmol Vis Sci* 1981; **21**: 669–80.

9 Scadding JG, Mitchell DN. *Sarcoidosis.* London: Chapman and Hall, 1985: 414–43.

10 Lehner T, Almeda JD, Levinsky J. Damaged membrane fragments and immune complexes in the blood of patients with Behçet's syndrome. *Clin Exp Immunol* 1978; **34**: 206–12.

11 Andrews BS, McIntosh J, Petts V, Avery R. Circulating immune complexes in retinal vasculitis. *Clin Exp Immunol* 1977; **29**: 23–9.

12 Nussenblatt RB, Gery I, Ballintine EJ, Wacker WB. Cellular immune responsiveness of uveitis patients to retinal S antigen. *Am J Ophthalmol* 1980; **89**: 173–9.

13 Dumonde DC, Kasp Grochowska E, Banga JP, *et al.* Autoimmune mechanisms in inflammatory eye disease. *Trans Ophthalmol Soc UK* 1985; **104**: 232–8.

Accepted for publication 25 March 1987.

British Journal of Ophthalmology, 1988, **72**, 448–451

Conjunctival anaerobic and aerobic bacterial flora in paediatric versus adult subjects

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SUMMARY Although the bacterial flora of the conjunctiva in children and adults has been studied, there has been no previous comparison between these two age groups of anaerobic as well as aerobic bacteria. Conjunctival cultures from 229 eyes of 144 uninfected subjects were analysed for aerobic, microaerophilic, and anaerobic bacteria. Adults showed a greater number of species per eye than did younger subjects (1·47 versus 1·13; $p<0.05$). Anaerobic species, predominantly *Propionibacterium*, were obtained from 27·1% of all eyes, but from a significantly greater percentage (30·2% versus 12·8%) of adults' than children's eyes ($p<0.04$). *Streptococcus* spp. were cultured from 14·9% of the children's eyes as opposed to only 2·2% from adults ($p<0.005$). Understanding the differences in conjunctival flora between normal adults and children aids the interpretation of culture results and leads to properly defining and treating potential pathogens.

The presence of micro-organisms in the normal human conjunctiva was established in the 19th century.[1] Since that time the normal aerobic flora of the adult human conjunctiva has been studied by numerous authors from various countries.[2-4]

More recently, improved microbiological techniques have allowed the isolation and delineation of anaerobic bacteria whether normal residents of the ocular surface or potential ocular pathogens.[5-8] The relatively few reports on the frequency of anaerobic colonisation of the normal conjunctiva have shown conflicting results. While some investigators[5-7] have reported as many as 80% of normal human conjunctivae to be colonised by anaerobes, others have found few or none.[3 9 10] The only modern series to compare the bacterial flora of children with that of adults studied only aerobic bacteria.[3] To study these issues we have compiled the first series to compare both aerobic and anaerobic conjunctival bacterial floras in children and adults.

Materials and methods

One hundred and forty-four patients undergoing ophthalmic surgery were studied. Their ages ranged from 6 months to 95 years. Children were defined as those aged 17 years or less. No patient had an active infection or obstructed lacrimal outflow system at the time of study. No antibiotics or other medications were applied to the eye prior to study for at least four weeks. A sterile, anaerobic transport, dry swab was applied to the inferior conjunctival fornix of each eye.

Each culture swab was washed three times in 0·5 ml of Schaedler's broth, and manually vortexed repeatedly after being wrung out by pressing it along the sides of the tube. The swab was cultured in 10 ml of Schaedler's broth. Blood and chocolate agar plates were inoculated with 0·1 ml of eluant, which was spread on the surface of the agar with a glass rod. The blood agar plates which contained brain-heart infusion agar base (BBL, Baltimore, MD), 5% sheep blood supplemented with vitamin K, and Filde's enrichment were incubated for at least seven days at 35°C in an anaerobic jar with a gas mixture of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen. Chocolate agar plates (Scott, Carson, CA) were incubated with 5% to 10% carbon dioxide at 35°C for at least seven days. After incubation the colonies were differentiated and enumerated by standard bacteriological techniques, including the VPI technique for anaerobic bacteria.[10]

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Results

The mean numbers (±SD) of colonies and species per eye are presented in Table 1. The number of colonies isolated per eye was not significantly different statistically between children and adults. The number of different species isolated per eye was significantly higher in adults than in children (1·47 versus 1·13; p<0·05). Anaerobic species, predominantly *Propionibacterium acnes*, were obtained from 27·1% of eyes overall, but from a significantly higher percentage of the adults' than the children's eyes (30·2% versus 12·8%; p<0·04 by Fisher's exact test).

Positive culture results delineated by species are shown in Table 2. Sterile eyes (with no growth of bacteria from the conjunctiva) are not included in Table 2. The percentage of sterile eyes was similar in both groups (23% in younger subjects and 21% in adults). Streptococcus species were cultured from 14·9% of children's conjunctivae as opposed to only 2·2% of adults' (p<0·005 by χ^2 test). Culture results were otherwise similar between the two groups.

Table 1 *Results of cultures (mean±SD)*

	Children	*Adults*	*Total*
No. of patients	25	119	144
No. of eyes	47	182	229
No. of sterile eyes	11	39	50
No. of aerobic cultures	47	212	259
No. of anaerobic cultures	6	56	62
No. of colonies per eye	322±824	439±1329	
No. of species per eye*	1·13±0·89	1·47±1·08	

*p<0·05 by *t* test.

Table 2 *Species of bacteria isolated and fraction of total isolates*

	Children	*Adults*	*Total*
Bacillus subtilis	1 (2%)	0	1
Corynebacterium species	1 (2%)	14 (5%)	15
Diphtheroids	16 (30%)	68 (25%)	84
Haemophilus influenzae	0	5 (2%)	5
Micrococcus species	0	2 (1%)	2
Penicillium	0	1 (0·4%)	1
Proteus species	0	2 (1%)	2
Serratia marcescens	0	1 (0·4%)	1
Staphylococcus aureus	3 (6%)	7 (3%)	10
Staphylococcus epidermidis	19 (36%)	108 (40%)	127
*Streptococcus species**	7 (13%)	4 (1%)	11
True anaerobes:			
Peptococcus	0	1 (0·4%)	1
*Propionibacterium acnes***	6 (11%)	55 (21%)	61
Total no. of isolates	53	268	321
Total no. of eyes	47	182	229

*p<0·005 by Fisher's exact test.
**p<0·04 by Fisher's exact test.

Discussion

The aerobic bacterial flora of the normal adult human conjunctiva has been studied by numerous authors during the past 50 years.[2–4 9 11–13] These reports have shown remarkable consistency across time and geographic space. From these studies certain conclusions can be drawn. Most eyes harbour *Staphylococcus epidermidis*, with diphtheroids only somewhat less common. While other species are less usual, there are a few noteworthy exceptions. Locatcher-Khorazo and Seegal[3] reporting on cultures obtained from 10 271 individuals between 1952 and 1968 noted a 42% frequency of *Staphylococcus aureus* colonisation. Orfila and Courden[2] reported a prevalence of 11·6% Gram-negative rods in an Algerian population. Cason and Winkler[12] cultured streptococcus species from less than 1% of their patients in Birmingham, Alabama. Soudakoff[4] in 1954 cultured diphtheroids from only 2·8% of eyes in his Los Angeles based series. The type of aerobic flora of adult conjunctivae in our study is consistent with the majority of published reports.

Two modern studies have addressed the question of conjunctival flora variation with age. Khorazo and Thompson[14] reported no differences other than an increasing frequency of diphtheroids after age 50. The larger series reported by Locatcher-Khorazo and Segal[3] showed a lower incidence of diphtheroids in subjects below 18 years of age. Our data show no difference in the prevalence of diphtheroids between children and adults. However, since we studied a smaller population and did not distinguish between younger and older adults, we may have missed a trend toward increased numbers of diphtheroids in the elderly.

In a study of conjunctivitis in paediatric patients Brook studied the normal aerobic and anaerobic flora in some paediatric patients as controls.[15] There are some striking similarities between his data and ours. As in our study, Brook found *Propionibacterium* and *Peptococcus* to be the most common anaerobic bacteria and *Staphyloccocus epidermidis* to be the most common aerobic. From his data one can calculate that the average number of species isolated per paediatric patient was 1·1, which is virtually identical to our findings. The two studies differed in Brook's finding *Corynebacterium*, and not diphtheroids as we found, to be the second most common aerobe. Brook did not compare his data with any from an adult population.

Our study found a highly significant difference (p<0·002) in the prevalence of streptococcus species found in children's and adults' conjunctivae (14·9% versus 2·2%). Streptococcal colonisation of both skin[16] and upper respiratory tract[17] is known to be more frequent in children than in adults. Since these sites are believed to be an important source of conjunctival flora,[3] one might expect more streptococci in the conjunctivae of children as well.

Anaerobic bacteria were first reported in the normal conjunctiva by Haenel *et al.*[18] Nagata[19] in 1963 isolated and identified *Propionibacterium* species. Bachrach and colleagues[9] were unable to culture any anaerobic organisms in a series of 277 young adults. This inability may have resulted from failure to use enriched, solid-culture media and to incubate for at least seven days in order to maximise the yield of these often fastidious, slow-growing species.

Anaerobic bacteria are proved aetiological agents in all major forms of ocular and periocular infections.[8] Anaerobes such as *Actinomyces, Arachnia, Bacteroides, Bifidobacterium, Clostridium, Eubacterium, Lactobacillus, Peptococcus, Peptostreptococcus,* and *Propionibacterium* have been cultured from uninfected ocular tissue. These anaerobic bacteria have also been reported to be ophthalmic pathogens.[8] Some anaerobic ocular pathogens such as *Fusobacterium, Butyrovibrio,* and *Veillonella* have never been reported as normal flora. We now report normal anaerobic flora, primarily *Propionibacterium*, from 27·1% of all eyes in our study.

One of the main sources of conjunctival bacteria is the adjacent skin. Since *Propionibacterium* is the predominant anaerobic organism of the skin, it is understandable that it should play the same role in the conjunctiva.[8] Leyden and colleagues showed *Propionibacterium* to be present on the facial skin of every one of the 342 individuals tested and to be in much greater concentration after 20 years of age.[20] They attributed the age related changes in *Propionibacterium* concentration on skin to the greater production of sebum, as androgen secretion increases in adulthood. Sebum would supply nutrients such as triglycerides and free fatty acids to the resident bacteria. This is consistent with our finding of *Propionibacterium* in a significantly higher percentage of the conjunctivae of adults than children.

The differences in the conjunctival flora between adults and children may be explained by several potential mechanisms. These include age-related changes in general immune responsiveness, tear composition and dynamics, patterns of exposure to bacteria, past antibiotic utilisation, and the flora of adjacent areas such as skin and upper respiratory tract. Our study demonstrates that adults' eyes harbour more different species per eye than children's eyes (1·47 versus 1·13; $p<0·05$). Our data suggest that there are also more total microbial colonies per eye in adults than in children; however, the difference did not achieve statistical significance because of the large standard deviations encountered.

Studies on the frequency of normal conjunctival sacs which are sterile have shown marked disparity. At the low end of the spectrum, Perkins and colleagues,[7] Chang,[11] Matuura,[6] and Locatcher-Khorazo and Seegal[3] respectively reported 9·4%, 9%, 2·5%, and 0% of conjunctivae to be sterile. At the upper end Bachrach *et al.*,[9] Debnath,[21] McNatt *et al.*,[5] and Smith[13] reported 33%, 30%, 39%, and 47% respectively to be sterile. Our series reports 22% of conjunctivae sterile to both aerobic and anaerobic culture, with no significant difference between children and adults. This is of particular concern to the ophthalmologist when planning surgery, since sterility at the time of surgery presumably decreases the frequency of postoperative infections. It has been shown that with aggressive preoperative preparation, consisting of broad-spectrum topical antibiotics and skin and conjunctival application of diluted povidone-iodine solution, the percentage of sterile conjunctival sacs can be increased to 83%.[22] Other frequently used methods of preoperative antimicrobial preparation are less effective.[23 24]

We believe that a thorough understanding of the differences in conjunctival flora between paediatric and adult subjects is essential for the ophthalmologist. This knowledge has an important role both in the interpretation of clinical culture results and in the management of potential pathogens colonising the ocular surface.

References

1 Lawson A. The bacteriology of the normal conjunctival sac, and its practical bearing on the utility of antiseptics in ophthalmic surgery. *Br Med J* 1898; ii: 486–7.

2 Orfila J, Courden B. Contribution a l'étude de la flore conjunctivale normale. *Ann Oculist (Paris)* 1961; 194: 892–9.

3 Locatcher-Khorazo D, Seegal BC. *Microbiology of the eye.* St Louis: Mosby, 1972: 13–7.

4 Soudakoff PS. Bacteriologic examination of the conjunctiva. *Am J Ophthalmol* 1954; 38: 374–6.

5 McNatt J, Allen SD, Wilson LA, Dowell VR. Anaerobic flora of the normal human conjunctival sac. *Arch Ophthalmol* 1978; 96: 1448–50.

6 Matuura H. Anaerobes in the bacterial flora of the conjunctival sac. *Jpn J Ophthalmol* 1971; 15: 116–24.

7 Perkins RE, Kundsin RB, Pratt MV, Abrahamsen I, Leibowitz HM. Bacteriology of normal and infected conjunctiva. *J Clin Microbiol* 1975; 1: 147–9.

8 Jones DB, Robinson NM. Anaerobic ocular infections. *Ophthalmology* 1977; 83: OP309–31.

9 Bachrach U, Gurevitch J, Landau J, Birnbaum D. The flora of the normal conjunctiva of healthy people in Israel. *Acta Med Oriental* 1953; 12: 10–3.

10 Holdeman LV, Cato EP, Moore WEC. *Anaerobe Laboratory Manual.* Blacksburg: VPI Anaerobe Laboratory, 1977.

11 Chang WL. Bacteria flora of the normal conjunctiva. *Chin Med J* 1957; 75: 233–5.

12 Cason L, Winkler CH. Bacteriology of the eye. *Arch Ophthalmol* 1954; 51: 196–9.

13 Smith CH. Bacteriology of the healthy conjunctiva. *Br J Ophthalmol* 1954; **38:** 719–26.

14 Khorazo D, Thompson R. The bacterial flora of the normal conjunctiva. *Am J Ophthalmol* 1935; **18:** 1114–6.

15 Brook I. Anaerobic and aerobic bacterial flora of acute conjunctivitis in children. *Arch Ophthalmol* 1980; **98:** 833–7.

16 Somerville DA. The effect of age on the normal bacterial flora of the skin. *Br J Dermatol* 1969; **81** (suppl 1): 14–22.

17 Masters PL, Brumfitt W, Mendez RL. Bacterial flora of the upper respiratory tract in Paddington families, 1952–4. *Br Med J* 1958; iv: 1200–5.

18 Haenel H, Feldheim G, Muller-Beuthow W. Zur mikrobiologischen Ökologie des Menochen. *Zentralbl Bakteriol Mikrobiol* 1958; **172:** 73–92.

19 Nagata M. Corynebacterium in conjunctival sac. *Nitsuseki Igaku* 1963; **16:** 115–27.

20 Leyden JL, McGinley KJ, Mills OH, Kligman AM. Age-related changes in the resident bacterial flora of the human face. *J Invest Dermatol* 1975; **65:** 379–82.

21 Debnath SC. Effect of preoperative antibiotics on bacterial colony counts of the conjunctival sac. *J Ocul Ther Surg* 1985; **4:** 122–4.

22 Isenberg SJ, Apt L, Yoshimori R, Khwarg S. Chemical preparation of the eye in ophthalmic surgery. IV. Comparison of povidone-iodine on the conjunctiva with a prophylactic antibiotic. *Arch Ophthalmol* 1985; **103:** 1340–2.

23 Isenberg SJ, Apt L, Yoshimori R. Chemical preparation of the eye in ophthalmic surgery. I. Effect of conjunctival irrigation. *Arch Ophthalmol* 1983; **101:** 761–3.

24 Apt L, Isenberg SJ, Yoshimori R, Paez JH. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Arch Ophthalmol* 1983; **101:** 764–5.

Accepted for publication 25 March 1987.

British Journal of Ophthalmology, 1988, **72**, 452–455

Incontinentia pigmenti: the development of pseudoglioma

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SUMMARY A case is described of incontinentia pigmenti in an infant with relatively normal retinae at seven days after birth who went on to total blindness by three months. This was due to excessive neovascularisation of retinae and vitreous, leading to bilateral pseudoglioma.

Incontinentia pigmenti (Bloch-Sulzberger syndrome) is a generalised ectodermal and mesodermal dysplasia affecting eyes, skin, hair, nails, teeth, bones, and central nervous system. It nearly always affects females. It appears at or very soon after birth. The skin lesions start as a generalised blistering rash with vesicles or bullae on trunk and limbs. These heal and leave typical pigmented lines and whorls and sometimes verrucous lesions. The pigment comes from melanin granules which migrate from the epidermis into the dermis, where they are either free or absorbed by chromatophores.

The disease causes blindness, total or partial, in 25% to 35% of cases.[1] This paper describes the condition from one week after birth to the fully developed pseudoglioma.

Case history

A girl, a first baby, was born at 41 weeks gestation, birth weight 3·1 kg. Both parents were normal and there was no consanguinity. At 8 hours after birth she developed a generalised blistering rash suggestive of incontinentia pigmenti. At age 3 days she had twitching of her right arm and leg. Her skin progressed through the typical changes of incontinentia pigmenti, with linear pigmented lines on the trunk and the limbs and some verrucous lesions. The diagnosis was confirmed by biopsy.

At age 1 week (first ocular examination) the fundi showed dilated retinal veins in both eyes, with a small area of neovascularisation and exudates along the course of the left superior temporal retinal artery and vein above the macula (Fig. 1).

At 5 weeks the irides were vascularised. The retinal veins were now grossly dilated (×3) and tortuous, and there was extensive neovascularisation and oedema round the discs and the posterior pole (Figs. 2 and 3), but there was very little neovascularisation in the peripheries.

At 10 weeks there was increased vascularisation of the irides. The neovascularisation of the retinae and vitreous had massively increased, with vitreous haze and fibrosis in both eyes (Fig. 4).

At 13 weeks the vitreous haze had increased so that there was only a temporal red reflex in the right eye and no red reflex in the left. The retrolental membranes were almost total in the right eye and total in the left. The picture was now that of bilateral pseudoglioma.

Treatment was attempted with small doses of ACTH (5 units alternate days) from 2 to 5 months of age, but this was without any effect.

The child continued to have gross mental retardation, spasticity, and fits, and was totally blind, with bilateral retrolental membranes and a secondary cataract in the left eye.

Discussion

Incontinentia pigmenti was first described by Bloch[2] and Sulzberger.[3] In 1976 Carney[1] found 464 references in the world literature, including 653 valid case reports. The skin lesions occur in all cases, and have been outlined above. Abnormalities of the central nervous system occur in over 30%[1] and include epilepsy, spasticity, mental retardation, microcephaly, and hydrocephaly.

Dental abnormalities are seen in 65% of cases.[1] Some teeth are absent, others being pegged and malformed. Abnormalities of bone occur in more

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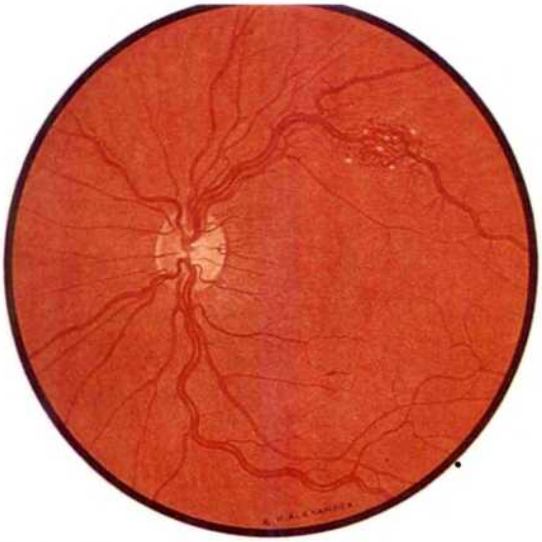

Fig. 1 *Left fundus at age 1 week, showing dilated retinal veins and one area of neovascularisation and exudates.*

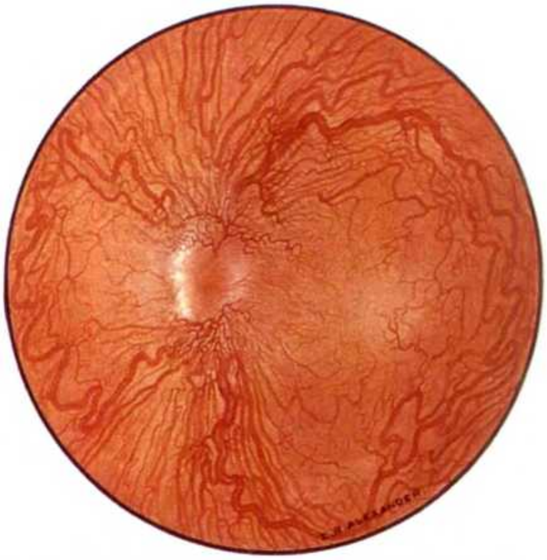

Fig. 3 *Left fundus at age 5 weeks, showing dilated tortuous retinal vessels and neovascularisation of disc and retina.*

than 20% of cases (skull deformities, kyphoscoliosis) and other congenital abnormalities (dwarfism, cleft palate, etc.) in 14%.

The ocular abnormalities are among the most important. Findlay[4] found an incidence of 32%, Scott *et al.*[5] found 26%, and Carney[1] found 18·9% with serious visual defects and 15% with milder defects.

The serious ones are pseudoglioma, retinal detachment, optic atrophy, cataract, microphthalmos, and phthisis bulbi.[4-6] The milder changes include exudative choroiditis,[7] peripheral retinal changes,[8-10] nystagmus, strabismus, and myopia.

The early retinal changes have been described by Findlay,[4] Lieb and Guerry,[7] and Nishimura *et al.*[10] Findlay described a case at age 2 months with dilated retinal and choroidal vessels in one eye and a greyish

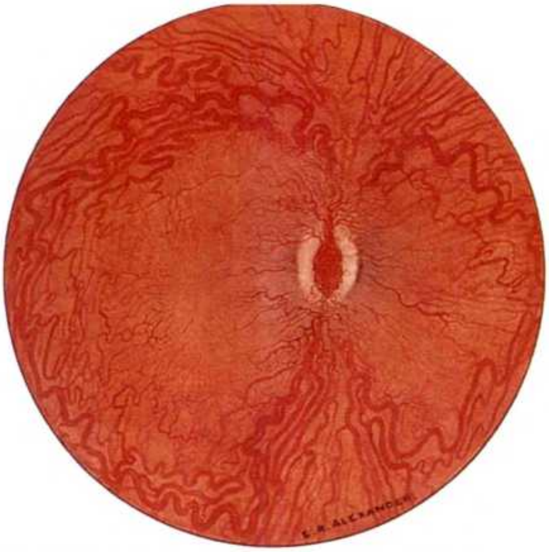

Fig. 2 *Right fundus at age 5 weeks, showing dilated tortuous retinal vessels and neovascularisation of disc and retina.*

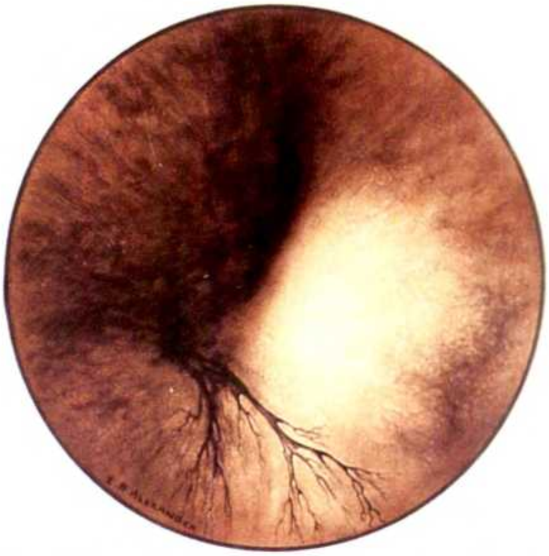

Fig. 4 *At age 10 weeks an ophthalmoscopic view of the left vitreous showing neovascularisation and fibrosis.*

retinal elevation in the periphery. At 6 months this baby had a nasal retinal detachment and retrolental mass in that eye, and the other eye was normal.

Lieb and Guerry[7] described a case at age 4 weeks with dilated retinal veins and pannus-like vascularisation at the posterior pole in one eye, and retinal oedema and corkscrew vessels at the macula in the other. One eye went on to develop an 'exudative choroiditis' at the macula, with neovascularisation and star-shaped exudates.

Nishimura *et al.*[10] observed one case from the thirteenth day, when the retinal vessels were fairly normal but there was some retinal oedema. At age 34 days the retinal venules became dilated and tortuous, vascular anastomoses developed at the equator, and the peripheral retina appeared avascular. Further neovascularisation occurred at 62 days in the left eye but the right became normal. At 78 days photocoagulation was applied to prevent further vascular proliferation in the left eye. At 1 year the right eye was comparatively normal but in the left there was optic atrophy and pigmentary degeneration at the macula and general constriction of the retinal vessels.

These three cases showed early changes similar to the one described here but they were less severe and only one[4] went on to develop a partial pseudoglioma.

Later retinal changes were described by Watzke *et al.*[8] In 19 cases all over the age of 2 years they found five with unilateral and two with bilateral zones of abnormal arteriovenous anastomoses and preretinal fibrosis at the temporal equator, and no retinal perfusion temporal to it. Jain and Willetts[9] described a case in a girl who had had incontinentia pigmenti from birth and at the age of 14 years had microaneurysms temporal to the macula and retinitis proliferans in the upper temporal equator.

Other retinal changes include abnormalities of the pigment epithelium, glial strands, haemorrhagic and pigmentary retinitis, retinal dysplasia, and retinal detachment. François[11] surveyed the literature of retinal changes in incontinentia pigmenti and added two cases with ocular changes, one with retinal detachment and one with optic atrophy and squint.

In the present case the pathological process consisted of a dilatation of the retinal and choroidal circulations starting 1 week after birth, followed at 5 weeks by dilated tortuous retinal vessels and neovascularisation of the retina and disc in both eyes. By 10 weeks the new vessel formation had spread forwards into the vitreous, leading to bilateral pseudoglioma by 13 weeks. The child had the general signs of a severe form of the disease with extensive ocular, neurological, skin, and dental involvement.

Watzke *et al.*[8] state that 'it may be that pseudoglioma is the end stage of this retinal vascular abnormality'. Similarly François[11] states that 'pseudoglioma is probably the end stage of the retinal vascular changes'. The case described here is proof of this sequel of events.

The cause of the vascularisation remains obscure. In recent work on kittens' retinae Taylor *et al.*[12] think they may have isolated the metabolite that stimulates new vessel formation in the eye, postulated by workers over the last 40 years.[13] They suggest that vascularisation may be stimulated by endothelial-cell stimulating angiogenic factor (ESAF). They found that ESAF, when measured quantitatively by procollagenase activation, was three times greater in the retinae of kittens subjected to prior excessive oxygen intake than in normal kittens. Watzke *et al.*[8] and Nishimura *et al.*[10] have noted retinal ischaemia in the periphery of the fundus with absence of perfusion in these areas (demonstrated by fluorescein angiography) beyond the equatorial areas of arteriovenous anastomoses and new vessel formation. This retinal ischaemia may well be the source of the angiogenic factor ESAF in this disease, and so be the cause of the extensive neovascularisation observed in this case in both the retinae and the irides, possibly following prior retinal ischaemia. Further research work along these lines may lead to advances in understanding and treating the ocular complications of incontinentia pigmenti.

I wish to thank Dr Beryl Corner and Dr Roger Harman, of Southmead Hospital, Bristol for referring this case, and Mr E R Alexander for the fundus paintings.

References

1. Carney RG. Incontinentia pigmenti. A world statistical analysis. *Arch Dermatol* 1976; **112:** 535–42.
2. Bloch B. Eigentümliche, bisher nicht beschriebene Pigmentaffektion (incontinentia pigmenti). *Schweiz Med Wochenschr.* 1926; **56:** 404.
3. Sulzberger MB. Über eine bisher nicht beschriebene congenitale Pigmentanomalie (incontinentia pigmenti). *Arch Dermatol Syph (Berlin)* 1928; **154:** 19–32.
4. Findlay GH. On the pathogenesis of incontinentia pigmenti, with observations on an associated eye disturbance resembling retrolental fibroplasia. *Br J Dermatol* 1952; **64:** 141–6.
5. Scott JG, Friedmann AJ, Chitters M, Pepler WJ. Ocular changes in the Bloch-Sulzberger syndrome (incontinentia pigmenti). *Br J Ophthalmol* 1955; **39:** 276–82.
6. Zweifach PH. Incontinentia pigmenti. Its association with retinal dysplasia. *Am J Ophthalmol* 1966; **62:** 716–2.
7. Lieb WA, Guerry D. Fundus changes in incontinentia pigmenti. (Bloch-Sulzberger syndrome). *Am J Ophthalmol* 1958; **45:** 265–71.
8. Watzke RC, Stevens TS, Carney RG. Retinal vascular changes of incontinentia pigmenti. *Arch Ophthalmol* 1976; **94:** 743–6.
9. Jain RB, Willetts GS. Fundus changes in incontinentia pigmenti (Bloch-Sulzberger syndrome): a case report. *Br J Ophthalmol* 1978; **62:** 622–6.
10. Nishimura M, Oka Y, Takagi I, Yamana T, Kitano A. The clinical features and treatment of the retinopathy of Bloch-Sulzberger syndrome (incontinentia pigmenti). *Jpn J Ophthalmol* 1980; **24:** 310–9.
11. François J. Incontinentia pigmenti (Bloch-Sulzberger syndrome) and retinal changes. *Br J Ophthalmol* 1984; **68:** 19–25.

12 Taylor CM, Weiss JB, Kissun RD, Garner A. Effect of oxygen tension on the quantities of procollagenase-activating angiogenic factor present in the developing kitten retina. *Br J Ophthalmol* 1986; **70**: 162–5.

13 Anonymous. Neovascularisation (Editorial). *Br J Ophthalmol* 1986; **70**: 161.

Accepted for publication 23 April 1987.

British Journal of Ophthalmology, 1988, **72**, 456–460

Metastasis of choroidal melanoma to the contralateral choroid, orbit, and eyelid*

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SUMMARY A 52-year-old woman was found to have a small juxtapapillary pigmented lesion in the choroid of the left eye. This lesion remained clinically stationary for one year, but subsequent growth prompted enucleation of the eye. The tumour was diagnosed histologically as a choroidal malignant melanoma of mixed cell type. Approximately 52 months later the patient developed proptosis of the contralateral (right) eye. Orbital ultrasonography showed a large mass in the right orbit, which was confirmed by needle biopsy to be a melanoma. In addition the patient was found to have metastatic melanoma to the choroid, right lower eyelid area, and liver. The development of simultaneous orbital, choroidal, and eyelid metastases from a contralateral choroidal melanoma is of ophthalmic interest and appears to be unique.

Metastatic disease from primary uveal malignant melanoma characteristically occurs in the liver and less commonly in the lung, subcutaneous tissues, and other organs.[1] Metastatic uveal melanoma to the opposite eye is extremely rare. We report a unique case of metastasis of a relatively small choroidal melanoma from the choroid of the left eye to the contralateral orbit, choroid, and eyelid.

Case report

A 52-year-old white woman had no prior ocular problems until April 1979 when she was found on routine examination to have a small juxtapapillary pigmented choroidal mass in the left eye. In October 1978 a fundus examination of both eyes by indirect ophthalmoscopy had shown no abnormalities. On our examination in April 1979 her visual acuity was 6/6 (20/20) in each eye, and the intraocular pressures were normal. The fundus of the right eye was carefully examined by indirect ophthalmoscopy, and there was no evidence of choroidal naevi or other fundus lesions.

In the left eye a moderately pigmented choroidal tumour extended superiorly from the optic disc margin; it measured approximately 6×5 mm in basal diameter and 2·5 mm in thickness (Fig. 1). There was a geographical distribution of orange pigment over the surface of the tumour. Fluorescein angiography

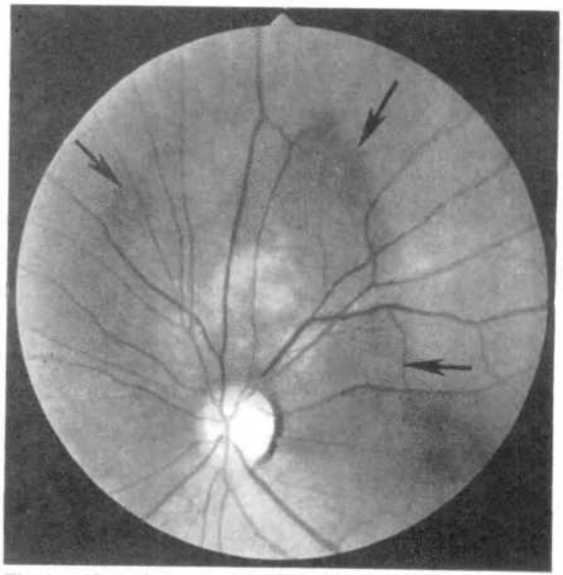

Fig. 1 *Clinical photograph of small peripapillary pigmented lesion (arrows) as seen on the initial visit.*

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*Presented at the Annual Meeting of the Atlantic Coast Fluorescein Club, Baltimore, 7 February 1986.

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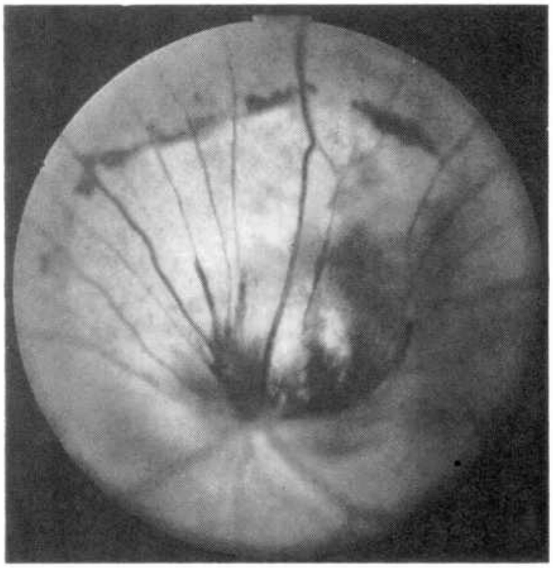


Fig. 2 *Fundus photograph of same lesion as shown in Fig. 1 after progressive growth. Note that the lesion is now obscuring the superior margin of the optic disc.*

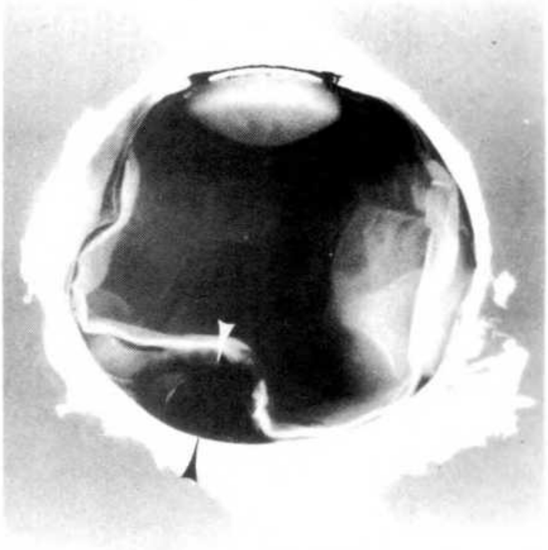


Fig. 3 *Grossly sectioned eye showing pigmented tumour in the posterior segment (arrows).*

showed early mottled fluorescence and late staining of the mass compatible with a suspicious naevus or small melanoma. Ultrasonography demonstrated a solid choroidal tumour with low internal reflectivity and a thickness of 2·5 mm.

These findings were compatible with a suspicious choroidal naevus or a small choroidal melanoma and the patient was followed up periodically. Examinations were performed every 4–6 months and the lesion remained unchanged. Ocular and general physical examinations revealed no other abnormalities.

On 14 October 1980 her visual acuity remained 6/6 in each eye but the tumour had become more elevated and extended over the superior margin of the optic disc (Fig. 2). Repeat ultrasonography

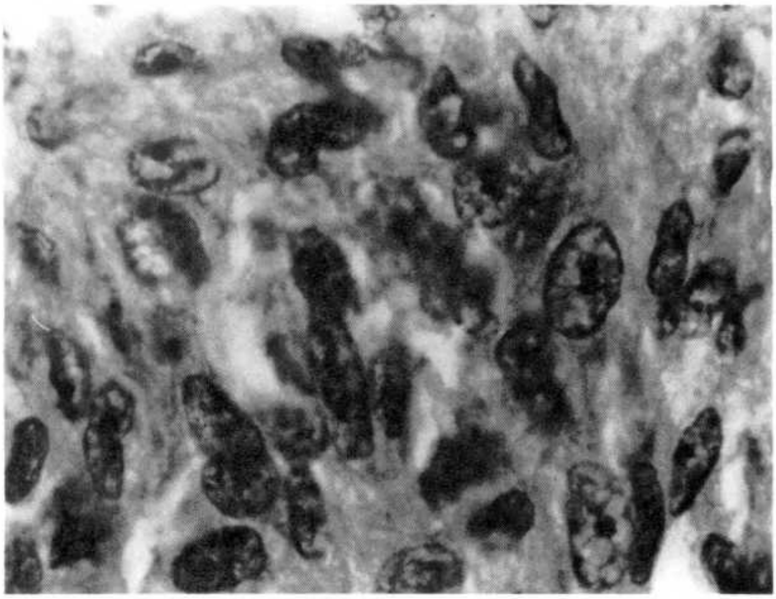


Fig. 4 *Histopathology of choroidal tumour showing predominance of spindle melanoma cells. Haematoxylin-eosin, ×250.*

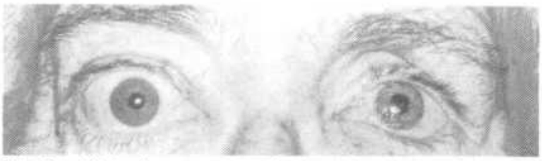


Fig. 5 *Clinical appearance of patient showing ocular prosthesis on the left and proptosis on the right side.*

showed the tumour to be 5·4 mm thick and to have low internal reflectivity and acoustic hollowness. An incisional P-32 test revealed a positive uptake of 175%. These findings were compatible with a choroidal malignant melanoma, and the eye was enucleated on the following day. A complete systemic evaluation prior to enucleation revealed no evidence of metastatic disease.

The sectioned eye had a dome shaped pigmented choroidal tumour arising near the optic nerve head (Fig. 3). There was a small nodule where the tumour had broken through Bruch's membrane and invaded the sensory retina. Microscopically the tumour proved to be a mixed-cell malignant melanoma with a predominance of spindle B cells (Fig. 4).

Follow-up examination in April 1981, October 1981, April 1982, and May 1983 showed the patient to be systemically normal with no evidence of metastatic disease or local recurrence. On 27 October 1983 her liver enzymes were found to be slightly raised, with a lactate dehydrogenase level of 249 IU/l (normal 100–225), a serum glutamic oxaloacetic transaminase level of 88 IU/l (normal 7–40) and a γ glutamyl transpeptidase level of 24 IU/l (normal 6–24). A systemic examination was recommended at that time, but the patient did not return for follow-up until 22 May 1984, at which time she complained of progressive epigastric pain and weight loss. She was noted to have tenderness of the right upper abdominal quadrant and pigmented lesions on the back and scalp. One of these was biopsied and found to be metastatic melanoma. A liver scan revealed multiple abnormal defects compatible with metastatic melanoma.

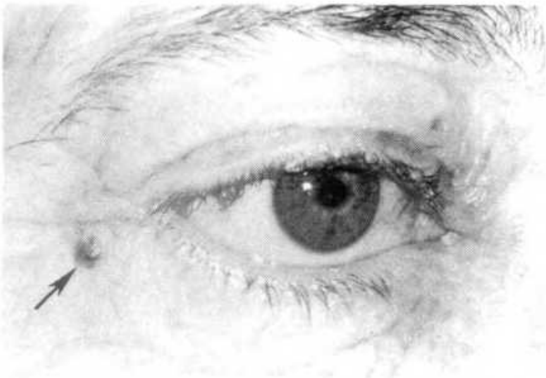


Fig. 7 *Clinical appearance of metastatic melanoma to lateral aspect of right lower eyelid (arrow).*

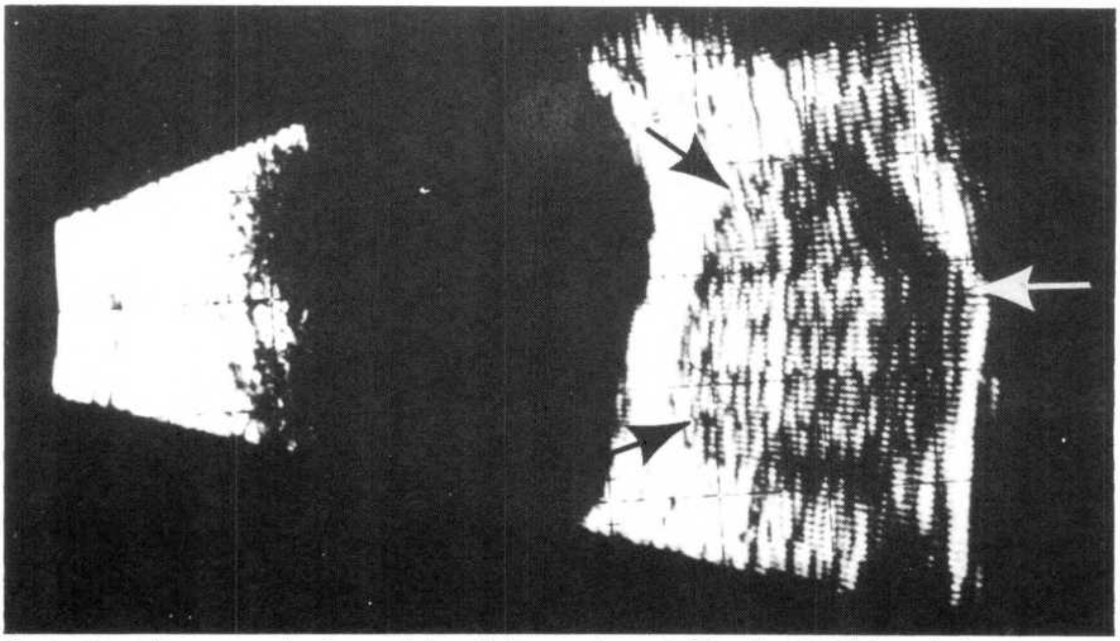


Fig. 6 *B scan ultrasonogram showing rounded retrobulbar mass (arrows) with moderately high internal reflectivity.*

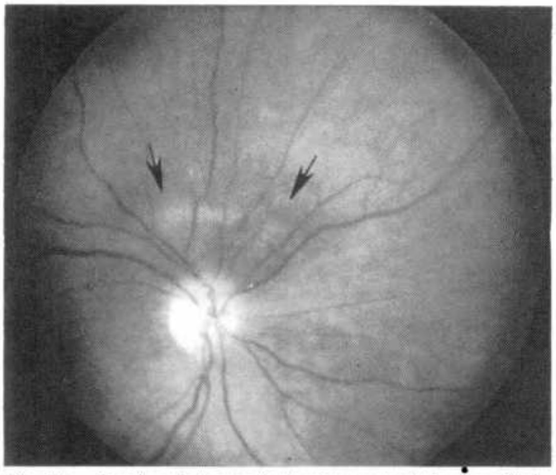


Fig. 8A *Fundus photograph showing metastatic choroidal melanoma superior to optic disc in the right eye (arrows).*

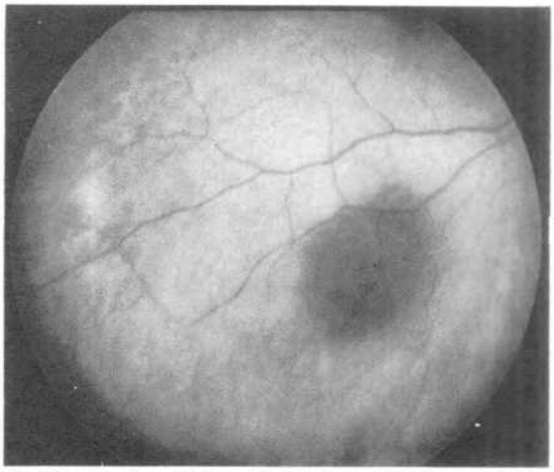


Fig. 8B *Fundus photograph showing metastatic choroidal melanoma inferotemporal to macular area in the right eye.*

The patient was treated by systemic chemotherapy and remained fairly stable until 18 April 1985, when she first noted prominence of her right eye. Examination disclosed 8 mm of proptosis (Fig. 5) of right eye by Hertel exophthalmometry. B scan ultrasonography showed a rounded retrobulbar mass with high internal reflectivity (Fig. 6). There was also a new black subcutaneous nodule in the lateral aspect of the right lower eyelid (Fig. 7). Fundus examination revealed prominent choroidal folds and two pigmented choroidal tumours, one superonasal to the optic disc and the other inferotemporal to the fovea (Figs. 8A, 8B). An orbital fine needle aspiration biopsy of the retrobulbar mass showed metastatic melanoma (Fig. 9).

It was recommended that the patient have continued chemotherapy and radiation to the right eye and orbit. However, this was never completed, and she died with liver failure on 16 May 1985. Permission for necropsy was not granted.

Discussion

With the exception of orbital extension of uveal melanomas, malignant melanomas of the orbit are extremely rare. Melanomas can secondarily extend directly into the orbit from the primary lesions in the uvea, conjunctiva, and eyelid.[1-3] Metastatic cutaneous melanoma to the orbit is quite rare. In the series of 764 orbital tumours reported by Henderson

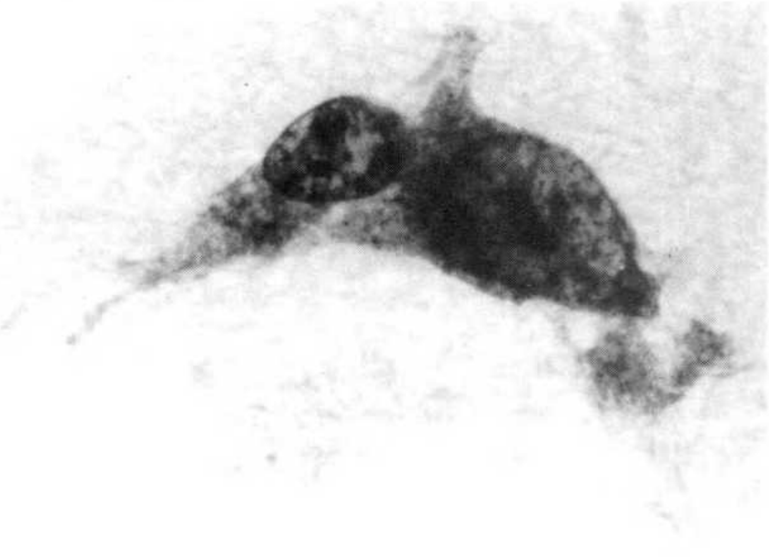


Fig. 9 *Cytology of fine needle aspiration biopsy showing anaplastic tumour cells with cytoplasmic melanin consistent with malignant melanoma cells. Papanicolaou, ×320.*

and Farrow there was one case of metastatic cutaneous melanoma to the orbit and no cases of metastatic uveal melanoma to the orbit.[4] In 1967 Font and associates recorded five cases of orbital involvement by metastatic cutaneous melanoma in the files of the Armed Forces Institute of Pathology.[5] In the series of 645 biopsied orbital masses reported by Shields and associates there were no cases of metastatic melanoma to the orbit.[6]

To our knowledge there have been only two reported cases in the English literature of choroidal melanoma metastatic to the opposite orbit.[7,8] In the case reported by Philps in 1949 an orbital metastasis developed approximately 10 years after enucleation of the opposite eye for a large choroidal melanoma.[7] In the case reported by Foster and associates in 1957 metastasis to the opposite orbit was noted approximately four years after enucleation of a uveal melanoma.[8]

Sceptics might argue that the eyelid, orbital, and choroidal melanomas in this case could represent metastases from either an undetected cutaneous melanoma or from an occult visceral melanoma. Metastatic cutaneous melanoma to the choroid, although quite rare, is well recognised.[5,9] Metastatic melanoma to the orbit has been known to occur from an occult primary melanoma in the colon.[10] However, our patient had thorough general examinations, and there was no evidence of a primary cutaneous or visceral melanoma.

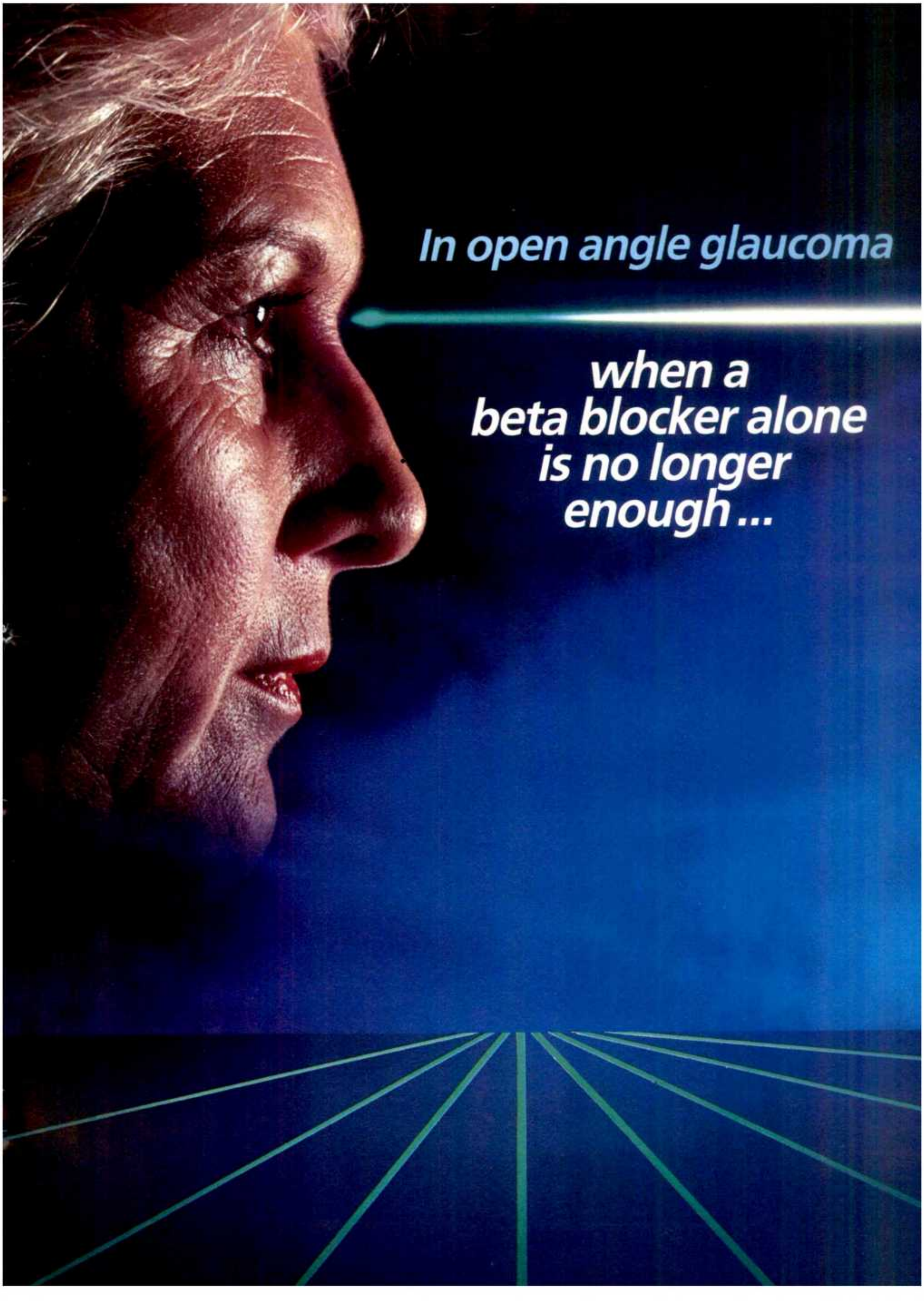
We are not aware of any prior well documented cases of metastatic uveal melanoma to the contralateral choroid. The case reported here appears to represent a well documented example of metastases from a relatively small but growing melanoma of the choroid to the contralateral orbit, choroid, and eyelid, as well as systemic metastases. It is possible that other patients with near terminal melanomatosis from uveal melanomas have metastatic foci to the opposite choroid or orbit, but that they are not subject to detailed ocular examination, and the metastatic foci remain subclinical.

This work was supported in part by the Ocular Oncology Fund, Wills Eye Hospital, in part by the Oncology Research Fund, Wills Eye Hospital, and in part by the Black Patch Invitational Golf Tournament, Downingtown, Pa, USA.

References

1 Shields JA. *Diagnosis and management of intraocular tumors.* St Louis: Mosby, 1983: chapter 7.
2 Shields JA, Augsburger JA, Corwin S, Donoso LA, DiSantis M. The management of uveal melanomas with extrascleral extension. *Orbit* 1986; **5:** 31–7.
3 Shields JA. Malignant melanomas involving the orbit. In: Hornblass A, ed. *Ophthalmic and orbital plastic and reconstructive surgery.* Baltimore: Williams and Wilkins, in press.
4 Henderson JW, Farrow GM. *Orbital tumors.* New York: Decker, 1980.
5 Font RL, Naumann G, Zimmerman LE. Primary malignant melanoma of the skin metastatic to the eye and orbit: report of ten cases and review of the literature. *Am J Ophthalmol* 1967; **63:** 738–54.
6 Shields JA, Bakewell B, Augsburger JJ, Flanagan JC. Classification and incidence of space-occupying lesions of the orbit. A survey of 645 biopsies. *Arch Ophthalmol* 1984; **102:** 1606–11.
7 Philps S. Choroidal sarcoma with metastasis in the opposite orbit. *Br J Ophthalmol* 1949; **33:** 732–9.
8 Foster J, Henderson W, Cowie JW, Harriman DSF. Choroidal sarcoma with metastasis in the opposite orbit. *Br J Ophthalmol* 1957; **41:** 42–7.
9 DeBustros S, Augsburger JJ, Shields JA, Shakin EP, Pryor C. Intraocular metastases from cutaneous malignant melanoma. *Arch Ophthalmol* 1985; **103:** 937–40.
10 Prasad VN, Bist HK, Narain M. Metastatic orbital malignant melanoma—a cause of unilateral proptosis. *Afro-Asian J Ophthalmol* 1984; **3:** 87–9.

Accepted for publication 15 April 1987.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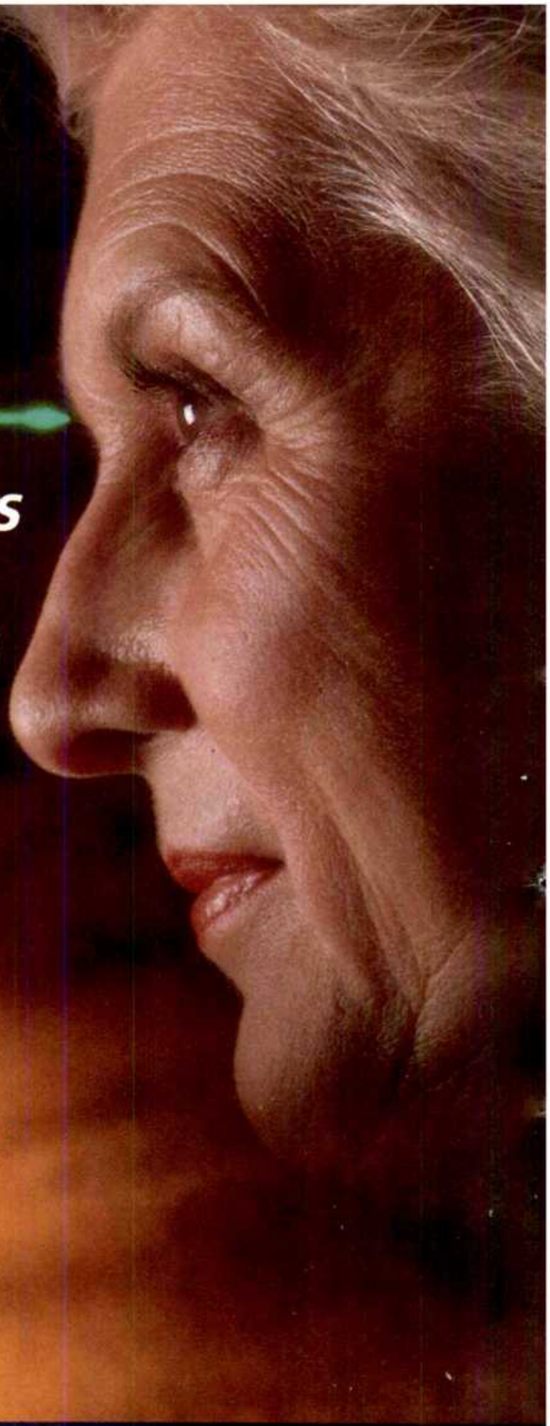

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Prostaglandin D_2 reduces intraocular pressure

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SUMMARY When PGD_2 was topically applied to the rabbit eye a reduction of intraocular pressure (IOP) was observed within 30 min. The IOP reduction lasted throughout the observation period of 7 hours. No increase of IOP was observed during the period. The effect of PGD_2 was dose-dependent (0·4 μg to 250 μg), and the minimum effective dose was estimated to be 2·0 μg. The application of PGD_2 did not affect the pupil diameter. No sign of inflammatory response was observed by PGD_2 application, that is, no hyperaemia, no flare, no irritation, and no increase of protein content in the aqueous humour. These results suggest that PGD_2 or its analogues may be useful for treating glaucoma.

Prostaglandins (PGs) are formed in the eye[1 2] following various kinds of stimulation and are thought to mediate inflammatory responses.[3] Among several types of PGs the PGE and F series have been extensively studied in relation to intraocular pressure (IOP).[4-9] Early studies showed that these compounds are hypertensive.[4] Recently, however, topical application of them was found to eventually lower the IOP in many animal species.[5-7] Yet higher doses induce an initial increase of the IOP in rabbits[5] and monkeys[6 7] and also cause aqueous flare in rabbits[6] and cats.[7]

More recently the effects of $PGF_{2\alpha}$[8] and its isopropyl ester[9] on the human eye have been examined; and these PGs were found, as in animal eyes, to reduce the IOP. However, several side effects such as initial hypertension from higher doses, conjunctival hyperaemia, headache, and ocular smarting were noted. Thus the clinical usefulness of these PGs as hypotensive agents is limited, as has already been pointed out.[8]

During the course of biochemical experiments on PG synthesis in ocular tissues we found that PGD_2 is the major PG formed in the rat ocular system.[10] This PG has been also reported to be synthesised in the rabbit eye.[1 2] The effect of PGD_2 on IOP has, however, not been fully studied. We now report that topically applied PGD_2 is effective in reducing the IOP without side effects in rabbit eyes.

Material and methods

Albino rabbits (weighing 2·0–2·5 kg at the start of experiment) were used. The animals were restrained in metal rabbit holders, and the IOP was measured with an Alcon applanation pneumatonograph after the topical administration of a local anaesthetic (0·4% oxybuprocaine). PGs were kindly supplied by Ono Central Research Institute (Osaka, Japan). They were dissolved in 50 μl of 100 mM potassium phosphate buffer (pH 7·3) and applied topically to one eye. For the maximum dose of 250 μg the PGD_2-sodium salt was prepared by addition of an equimolar amount of Na_2CO_3 dissolved in a minimum volume of water to PGD_2, and then the pH and concentration were adjusted with a buffer. The other eye received the same amount of the buffer alone. For the long-term experiment (over 7 h) PG was administered between 11 and 12 am. For the measurement of protein content in the aqueous humour one eye was designated as the control and the other was treated with PGs. Aqueous humour was then collected once from each eye with a needle. Protein content was determined according to Lowry *et al.*[11] with bovine serum albumin as a standard.

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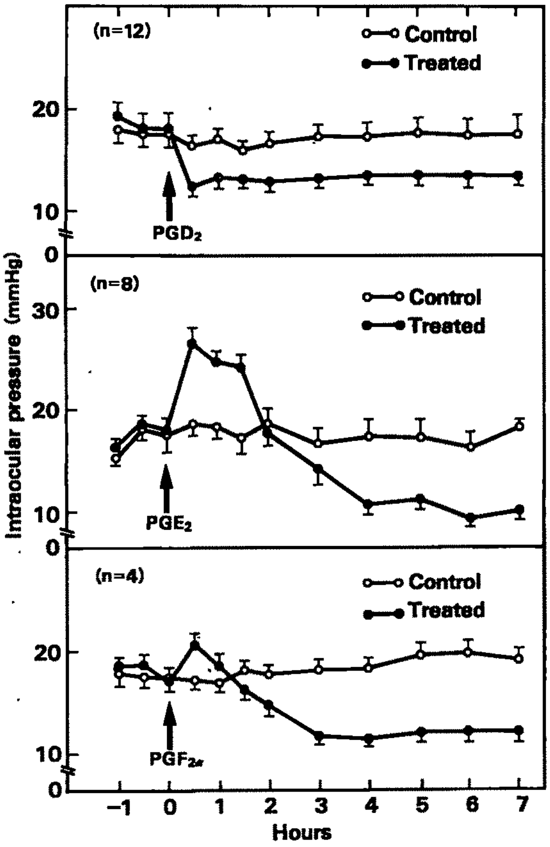

Fig. 1 *Effects of PGD_2, PGE_2, and $PGF_{2\alpha}$ on the IOP in rabbits. PGs (50 µg) were applied topically at 0 time (indicated by arrows). Each point shows the mean IOP, and the bars show the SEM.*

Results

Fig. 1 shows the effect of topical application of 50 µg of PGD_2, PGE_2, or $PGF_{2\alpha}$ on IOP. The effects of PGE_2 and $PGF_{2\alpha}$ at this dose were biphasic, as have been reported by several authors,[5,6] that is, application of either of these PGs resulted in an initial increase followed by a reduction in IOP. PGD_2 on the other hand did not cause any increase but only reduced IOP. The reduction of IOP by PGD_2 was observed within 30 min (but not at 15 min) and lasted throughout the observation period of 7 h. By 24 h, however, the IOP had returned to nearly its original level. The IOP at 24 h was 17·6±2·3 mmHg for the control and 17·7±2·0 mmHg for the treated eyes (n=9) (mean±SEM).

For four to seven hours after administration all three PGs reduced the IOP. As shown in Table 1, the mean IOP reduction during this period was the highest for $PGF_{2\alpha}$, followed by PGE_2 and PGD_2. However, since it is generally known that the initial IOP level has a significant influence on the magnitude of IOP reduction, we calculated R values to estimate the relative hypotensive effectiveness (Table 1). Judging from the R values, we considered PGE_2 to be the most effective agent for reducing IOP, followed by $PGE_{2\alpha}$ and PGD_2 under these conditions. The effect of PGD_2 on IOP was dose-dependent. No hypertensive phase was observed even with the maximum PGD_2 dose of 250 µg. The hypotensive effect reached nearly its maximum with 10 µg of PGD_2 (Fig. 2). The minimum dose effective in inducing a significant IOP reduction was judged to be

Table 1 *Comparison of hypotensive potency among PGD_2, E_2, and $F_{2\alpha}$*

	n	*Control IOP (mmHg)*	*Difference in IOP (mmHg)*	*R**
PGD_2	48	17·0±0·03	4·6±0·03	0·64±0·008
PGE_2	32	17·2±0·09	7·1±0·13	0·97±0·033
$PGF_{2\alpha}$	16	18·9±0·07	7·3±0·06	0·84±0·005

Data presented in this table were obtained during the hypotensive phase (4–7 h) after topical applications of 50 µg of the PGs. Means±SEM are given.

*R was calculated from the following equation: R=(IOPc−IOPt)/(IOPc−ESVP), where IOPc and IOPt are IOP in the control and in the treated eye respectively.

The episcleral venous pressure (ESVP) has been reported to be 10 mmHg.[12]

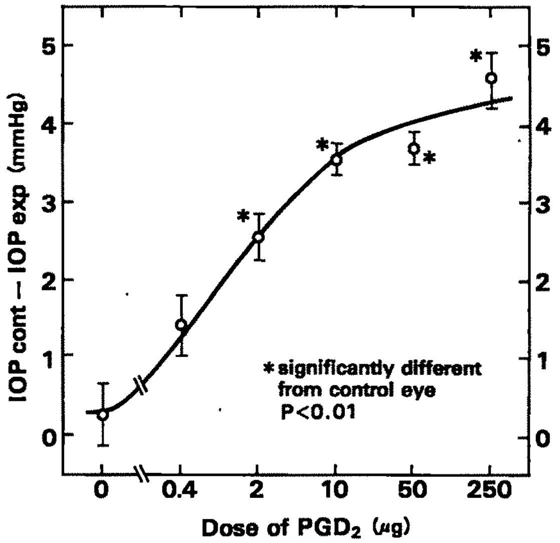

Fig. 2 *Effects of different doses of PGD_2 on IOP. Each point shows mean difference of IOP (IOP of control eye minus IOP of PGD_2 treated eye) obtained between 0·5 and 7 hrs after PGD_2 application. Bars indicate SEM. Statistical significance was determined by Duncan's multiple range test.*

Table 2 *Effects of PGs on protein content of the aqueous humour*

	n	*Protein content (g/l)*	
		Control eye	*Treated eye*
Control	3	0·62±0·04	0·69±0·09
PGD$_2$	3	0·67±0·09	0·58±0·04
PGE$_2$	3	0·58±0·04	23·07±1·54
PGF$_{2\alpha}$	4	0·63±0·08	2·61±0·94

The aqueous humour was collected 1 h after topical application of 50 µg of PG (buffer alone for the control group). Means±SEM are given.

2·0 µg. Interestingly, even after the maximum dose of PGD$_2$ (250 µg) was given, the IOP was reduced only to about 13 mmHg. On the other hand 50 µg of PGE$_2$ or PGF$_{2\alpha}$ reduced the IOP to 9–10 mmHg. The pupillary diameter was not affected even by 250 µg of PGD$_2$ for at least four hours after application.

No hyperaemia or flare was noted by slit-lamp examination during four hours after the application of up to 250 µg of PGD$_2$. However, PGE$_2$ and PGF$_{2\alpha}$ (50 µg) caused strong conjunctival and iridal hyperaemia and irritation (eyes tightly closed) within 30 min after the application. These inflammatory responses lasted for at least four hours. Flare was also noted during one to two hours after the application of PGE$_2$.

The effect of PGD$_2$ on the protein content in the aqueous humour was also different from that of PGE$_2$ or F$_{2\alpha}$. At one hour after application PGD$_2$ (50 µg) did not induce any elevation of the aqueous protein, while PGE$_2$ and F$_{2\alpha}$ caused a 40- and 4-fold elevation respectively (Table 2). PGD$_2$ failed to increase the aqueous protein not only at 1 h but also at later times after its application. Protein contents at 2, 4, and 6 h were 0·72±0·08 mg/ml (mean±SEM, n=4), 0·65±0·08 (n=4), and 0·59±0·03 (n=4), respectively, and did not differ from the control level.

Discussion

The effect of PGD$_2$ on IOP is distinct from that of PGE$_2$ or PGF$_{2\alpha}$. While 50 µg of PGE$_2$ or PGE$_{2\alpha}$ caused an initial elevation of IOP, PGD$_2$ (up to 250 µg) reduced IOP without any elevation phase. The effect of PGD$_2$ is also totally different from that of the other PGs in terms of inflammatory response. PGD$_2$ (up to 250 µg) caused no sign of inflammation, that is, no hyperaemia, no flare, and no irritation. At the dose of 50 µg PGD$_2$ did not cause an increase in the protein content of the aqueous humour, while the other two PGs induced a marked increase. Thus the action of PGD$_2$ on the eye appears to differ from that of the other two.

The hypertensive and inflammatory responses to PGE$_2$ or F$_{2\alpha}$ have been shown to be dose-dependent,[5-7] and lower doses of these two PGs have been reported to cause less inflammation and no hypertension.[5-7] In this experiment we have shown that the relative hypotensive potency of the three PGs is PGE$_2$>PGF$_{2\alpha}$>PGD$_2$. Therefore it is conceivable that PGD$_2$, being a weak agent, did not cause the initial IOP elevation or any inflammatory response. However, as our data show, the hypotensive effect of PGD$_2$ was saturated at about 10 µg, and a 25-fold increase in the PGD$_2$ dose did not induce any hypertensive or inflammatory response.

Our observations on the effects of PGD$_2$ on IOP and inflammatory responses differ from those reported by Kulkarni and Srinivasan,[13] who also used rabbits. They reported that either topical or intravitreal application of PGD$_2$ (10 µg) slightly raised the IOP of both eyes. In their experiment a five- to six-fold increase in the aqueous protein at three hours after application was also observed, but we did not find any such increase six hours after PGD$_2$ application. Although only a single dose experiment, PGD$_2$ (100 µg) topically applied to cats eyes is reported to decrease IOP.[14] A reduction in IOP by 10 to 50 µg of PGD$_3$ (an equivalent product from eicosapentaenoic acid to PGD$_2$ from arachidonic acid) has also been reported in rabbits.[15]

Species differences in PG-mediated responses are well documented. Therefore the results obtained in this study cannot necessarily be extended to the human eye. However, since PGD$_2$ was found to be effective in reducing the IOP without causing any sign of inflammatory response, it is worth examining PGD$_2$ or its analogues as therapeutic agents for the treatment of glaucoma in man.

We are grateful to Drs Y Watanabe, Y Urade, N Yumoto, M Hatanaka, and K Matsuda for useful discussions. Thanks are also due to Y Ueha and M Harada for secretarial assistance.

References

1 Battacherjee P, Kulkarni PS, Eakins KE. Metabolism of arachidonic acid in rabbit ocular tissues. *Invest Ophthalmol Vis Sci* 1979; **18:** 172–8.
2 Kass MA, Holmberg NJ. Prostaglandin and thromboxane synthesis by microsomes of rabbit ocular tissues. *Invest Ophthalmol Vis Sci* 1979; **18:** 166–71.
3 Mishima S, Masuda K. Prostaglandins and the eye: a review on clinical implications. *Metab Ophthalmol* 1979; **3:** 179–86.
4 Waitzman MB, King CD. Prostaglandin influences on intraocular pressure and pupil size. *Am J Physiol 1967;* **212:** 329–34.
5 Camras CB, Bito LZ, Eakins KE. Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits. *Invest Ophthalmol Vis Sci* 1977; **16:** 1125–34.
6 Lee P, Podos SM, Severin C. Effect of prostaglandin F$_{2\alpha}$ on aqueous humour dynamics of rabbit, cat and monkey. *Invest Ophthalmol Vis Sci* 1984; **25:** 1087–93.
7 Stern FA, Bito LZ. Comparison of the hypotensive and other ocular effects of prostaglandins E$_2$ and F$_{2\alpha}$ on cat and rhesus monkey eyes. *Invest Ophthalmol Vis Sci* 1982; **22:** 588–98.

8 Giuffré G. The effects of prostaglandin $F_{2\alpha}$ in the human eye. *Graefes Arch Clin Exp Ophthalmol* 1985; **222:** 139–41.
9 Alm A, Villumsen J. Intraocular pressure and ocular side effects after prostaglandin F_2 eye drops. A single dose-response study in humans. *Proc Int Soc Eye Res* 1986; 4: 14.
10 Goh Y, Urade Y, Fujimoto N, Hayaishi O. Content and formation of prostaglandins and prostaglandin-related enzyme activities in the rat ocular system. *Biochim Biophys Acta* 1987; **921:** 302–11.
11 Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with Folin phenol reagent. *J Biol Chem* 1951; **193:** 265–75.
12 Brubaker RF. Determination of episcleral venous pressure in the eye: a comparison of three methods. *Arch Ophthalmol* 1967; **77:** 110–14.
13 Kulkarni PS, Srinivasan BD. The effect of intravitreal and topical prostaglandins on intraocular inflammation. *Invest Ophthalmol Vis Sci* 1982; **23:** 383–92.
14 Bito LZ. Comparison of the ocular hypotensive efficacy of eicosanoids and related compounds. *Exp Eye Res* 1984; **38:** 181–94.
15 Kulkarni PS, Srinivasan BD. Prostaglandins E_3 and D_3 lower intraocular pressure. *Invest Ophthalmol Vis Sci* 1985; **26:** 1178–82.

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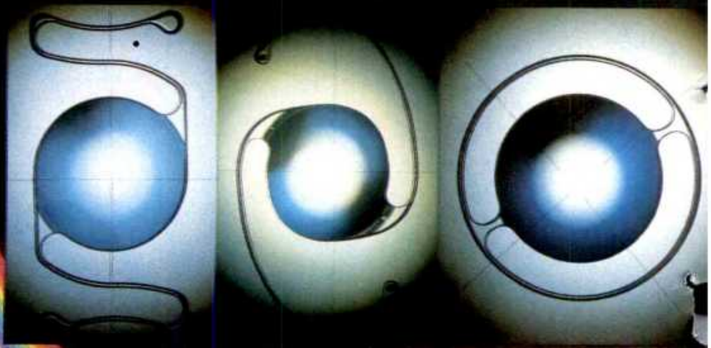

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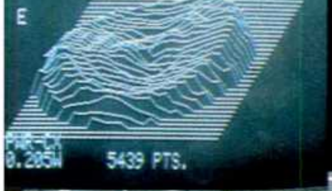

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British Journal of Ophthalmology, 1988, 72, 465–468

A single-blind randomised trial comparing adrenaline 1·0% with dipivalyl epinephrine (Propine) 0·1% in the treatment of open-angle glaucoma and ocular hypertension

K B MILLS AND N A JACOBS

From Manchester Royal Eye Hospital and Charing Cross Hospital, London

SUMMARY The results of this single-blind randomised trial comparing adrenaline 1% with dipivalyl epinephrine (Propine) 0·1% confirm that both have a significant effect in lowering the intraocular pressure in patients with open-angle glaucoma and ocular hypertension, but it is generally insufficient to warrant their use as the first line medical treatment of these two conditions. There was no significant difference between the intraocular lowering effect of the two preparations, and 60% of patients receiving Propine and 66% of those receiving adrenaline noted side effects.

Dipivalyl epinephrine (DPE, Propine) has recently become available in Britain for the treatment of open-angle glaucoma. It is an analogue of epinephrine (EPI). By the addition of two pivalic acid groups to the EPI molecules' hydroxyl sites DPE is rendered lipophilic and is absorbed into the eye up to 17 times more effectively.[1 2] When it penetrates the eye, corneal and aqueous esterases apparently[1 2] hydrolyse this analogue, converting it to the original EPI form. Because of this, DPE is referred to as a prodrug form of EPI.

Theoretically the advantage of improving penetration by whatever means is the lower concentration of drug required to achieve an equivalent therapeutic effect. The desirability of reducing the systemic and external ocular side effects of EPI is considerable. Many patients must discontinue EPI owing to orbital pain, allergic blepharoconjunctivitis, irritation, conjunctival hyperaemia, blurred vision, and corneal oedema.[3] Melanin related breakdown products of adrenaline may be deposited in the lower conjunctival sac. Cardiac arrhythmias and systemic hypertension are other hazards.[4] Aphakic cystoid maculopathy resulting from application of EPI would also be expected with the prodrug, as concentrations within the eye are equivalent.[5]

This trial was designed to compare the commonly used strengths of EPI (1%) and DPE (0·1%) with reference to both their ocular hypotensive and side effects.

Materials and methods

Patients with open-angle glaucoma controlled on topical therapy or selected at initial presentation, in addition to some with ocular hypertension, were included in this study. Patients with previous ocular surgery or who were taking any systemic therapy that may have an effect on intraocular pressure, such as systemic β-blockers or monoamine oxidase inhibitors, were excluded from the study.

After giving informed consent, 30 patients were randomly allocated to two groups. After a two-week washout period baseline intraocular pressure (IOP) recordings were taken (by Goldmann applanation tonometry). The resting blood pressure, pulse, and pupil size were also measured. The first group (mean age 70 years, 10 females and five males) received DPE 0·1% twice daily to each eye, while the second group (mean age 66 years, eight females and seven males) were given EPI 1% to be used similarly. At one month a full record of previously examined parameters was made, and at three and six months the IOP only was evaluated. These examinations

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were carried out between 1400 and 1500 h. Side effects were noted on all occasions. If the IOP exceeded 25 mmHg, the trial therapy was continued with the addition of pilocarpine 2% thrice daily. These patients were then observed for side effects. Trial therapy was discontinued in the event of severe side effects. Loss of control was defined as an IOP exceeding 22 mmHg. The pharmacy held the code, which was broken when all the patients had concluded this single-blind trial. The doctors were unaware of the code, hence unaware of the topical formulation, but the patients were aware of different eyedrops because the two sets of bottles of drops were not masked in any way.

At each follow-up visit individual patients were routinely asked whether they had experienced any redness of their eyes (conjunctival hyperaemia), ocular discomfort, blurred vision, or headache. They were also asked if there had been any other untoward reactions that they were concerned about. In addition any abnormal external eye findings on examination at each visit, including such findings as conjunctival hyperaemia, pigment deposition, and follicular reaction, were noted.

Results

The first group of 15 patients (DPE) included three ocular hypertensives. Their mean baseline IOP (Table 1) was 28·6 mmHg. For the second group (EPI), which included two ocular hypertensives, the mean baseline IOP was 29·8 mmHg. Thus the groups were comparable. The minimum IOP was 22 mmHg, and the maximum IOP asymmetry was 8 mmHg.

Table 1 *Baseline IOP values and IOP reductions at follow-up*

IOP (mmHg)	*DPE*			*EPI*		
	Mean (n)	*SD*	*p*	*Mean (n)*	*SD*	*p*
Baseline	28·6 (15)	4·7	—	29·8 (15)	4·9	—
One month	19·5 (14)	4·7	<0·0005	22·9 (15)	2·7	<0·0005
Three months	21·9 (11)	5·0	<0·005	22·8 (13)	3·0	<0·0005
Six months	22·7 (7)	3·8	<0·01	25·9 (10)	2·9	<0·025
Baseline for those completing six months	27·7 (7)	3·8		27·5 (10)	3·2	

n=Number of patients.
SD=standard deviation with Bessel's correction for small numbers.
p=Significance by unpaired one-tail Student's *t* test.

Table 2 *Breakdown of trial outcome*

Subgroup	*Total*	*No problems*	*Loss control*	*Side effects*	*Both*	*Other (see text)*
DPE six months completed	7	3	2	–	2	
DPE not completed	8	–		3	3	2
EPI six months completed	10	1	3	5	1	
EPI not completed	5	–	2	1	2	

Of the DPE group, only seven patients completed the trial. As four of these were not controlled on DPE alone, with two experiencing unacceptable side effects in addition (Table 2), a mere three patients were effectively managed on DPE. However, two of the eight patients not completing the trial were controlled at three months but were lost to follow-up, as one had a cataract extraction and another failed to continue the treatment. Significant side effects accounted for the other six, of whom three were also uncontrolled.

In the EPI group 10 patients completed the trial. With five patients experiencing unpleasant side effects, three more being uncontrolled, and another in both categories, one patient alone was satisfactorily managed on EPI. Of the five who failed to complete this trial two were uncontrolled, one experienced side effects, and a further two fell into both groups.

Table 1 shows the mean baseline IOP values and mean pressure reductions from baseline in each group at the study intervals. Further baseline values were calculated retrospectively for the patients who completed six months in each group, showing that these subgroups were still comparable. Statistical analysis of IOP reductions within the groups by the unpaired one-tail Student's *t* test revealed a highly significant fall for both groups at one month and three months, and a less marked but still significant lowering at six months. Comparing IOP reductions between the groups at each interval failed to demonstrate any significant difference by the unpaired two-tail Student's *t* test.

In Table 3 each group was divided into those with a baseline IOP of 30 mmHg or above and those with a baseline IOP of under 30 mmHg. As subgroup numbers were very low at six months, comparisons were made only for the first two intervals. At one month the fall of IOP in the high baseline DPE group was significantly greater (p<0·01) than in the low baseline DPE group, but at three months the difference was not significant (p<0·10). On the other hand no difference between EPI subgroups was seen at either interval. This is mirrored in the finding that the high DPE subgroup showed a significantly greater fall than the high EPI subgroup at one month (p<0·01), but by three months there was no significant difference (p<0·10).

Analysis of changes in pupil size, resting pulse, and blood pressure revealed no significant change from baseline within either group at one month. However,

Table 3 *Outcome of high and low baseline intraocular pressure subgroups*

IOP mmHg	*DPE ≥30 mmHg*			*vs*	*DPE <30 mmHg*				*EPI ≥30 mmHg*			*vs*	*EPI <30 mmHg*			
	Mean	*(n)*	*SD*		*Mean*	*(n)*	*SD*	*p*	*Mean*	*(n)*	*SD*		*Mean*	*(n)*	*SD*	*p*
Subgroup baseline	33·3	(6)	3·4		25·5	(9)	2·2		34·9	(6)	3·5		26·4	(9)	1·6	
Change at one month	−13·3	(6)	2·8		−5·9	(8)	3·1	<0·01	−7·2	(6)	2·1		−6·8	(9)	3·0	NS
Change at three months	−10·4	(4)	2·6		−3·6	(6)	4·5	NS	−7·6	(4)	3·4		−6·7	(9)	2·7	NS

n=Number of patients.
SD=standard deviation.
p=Significance by Student's *t* test.

differences between groups showed a significantly higher resting pulse rate in the DPE group at one month (p<0·005). Other comparisons did not reach significant values.

Although nine patients in the DPE group (60%) and 10 patients in the EPI group (66%) noted side effects, they have been recorded in descriptive categories (Table 4). Thus, if a patient complained of three effects, they would have been noted as three separate points. On average each DPE patient who complained had 1·44 side effects, and each EPI patient who complained had 1·8 side effects. Conjunctival hyperaemia was the most common problem, being more prominent in the EPI group, followed by ocular discomfort and blurred vision, more marked in the DPE group. Two patients in the EPI group noted severe episodes of shaking within 15 minutes of drop instillation.

Discussion

The outcome of this six-month trial using either topical DPE or EPI as first-line therapy in chronic glaucoma was disappointing. A residue of three DPE patients and one EPI patient with both good control and tolerable side effects from a total of 30 is difficult to defend. Two DPE patients were lost during the trial through no fault of the drug. Podos and Ritch,[5] however, advocate the use of EPI as initial treatment in open angle glaucoma. In the event of unpleasant side effects they recommend the substitution of DPE.

As DPE is superior to EPI in corneal penetration, a lower concentration should be required. Krieglstein and Leydhecker[6] found that, of various DPE concentrations, 0·1% was equivalent to 1% EPI. This strength of EPI was chosen, as 2% EPI offers no more in the long term.[7] In agreement with this, Bischoff[8] also noted that 0·1% DPE was comparable to 5% phenylephrine. A similar IOP reduction using 0·025% to 0·5% DPE was noted in ocular hypertensives,[3] without mydriasis at the lowest concentration. But a considerable loss of effect was apparent at one month. Two clinical studies compared DPE and EPI over three months[9] and over six months with a crossover midway.[10] They found DPE to be equally effective in IOP reduction,[9] and slightly less so particularly later on.[10] Different drugs were simultaneously applied to the fellow eyes of patients, and we consider that the humoral action of such a drug on the fellow eye following systemic absorption must compromise the significance of these results. Our results show a similar efficacy of the two drugs, with a trend towards reduced control by six months. Baseline IOP does not appear to be a useful predictor of therapeutic effect (Table 3), in spite of DPE's causing a significantly greater fall from high baseline IOPs at one month. A limitation on the clinical situation is introduced when patients with unacceptably poor IOP control are withdrawn from a trial. This necessarily leads to an overoptimistic value being quoted at later stages.

Table 4 *Incidence score of side effects for DPE and EPI*

Side effect	*DPE score*	*EPI score*
Conjunctival hyperaemia	3	7
Ocular discomfort	4	2
Blurred vision	4	2
Headache	1	2
Severe follicular reaction	1	1
Marked pigment deposition	0	1
Periorbital blanching	0	1
Shaking reaction	0	2
Total	13	18

Mydriasis tends to be mild and similar for the two drugs,[9 10] except that in one normal volunteer study it was less for DPE.[11] Pupil size in our investigation did not deviate significantly from baseline. Laboratory studies of cardiovascular effects following intravenous injection have shown a reduced and delayed response of catecholamines when in the dipivalyl form.[12] A sustet release action by enzyme conversion of DPE is proposed[13] for this delay. Other experimental work[14] has revealed that around 60% of both drugs are systemically absorbed after topical instillation, probably via the gastrointestinal tract. One clinical study[4] found an idiosyncratic rise in mean blood pressure for 25% of those patients on EPI, and increased ventricular ectopic beats in one case.

During the 'simultaneous drug' studies[9,10] mentioned earlier there was no pulse or blood pressure alteration from baseline. While in agreement with this, we detected a significantly higher ($p<0{\cdot}005$) resting pulse in DPE patients than in the EPI group rather than the baseline. Also two patients (Table 4) described an unpleasant shaking reaction 15 minutes after taking EPI.

Because there is little to choose between EPI and DPE as regards the ocular hypotensive and systemic effects, the main justification of DPE's higher cost must depend on improved ocular tolerance. Shorter assessments comparing uninterrupted use of the drugs for up to 3·6 months[9,10,15] have concurred that patients show a significantly greater ocular tolerance to DPE. Theodore and Leibowitz[16] noted that long-term exposure to DPE resulted in six of 26 patients becoming intolerant at between five and 22 months. Apart from the patients with conjunctival pigment staining, periorbital skin blanching, and a shaking reaction, ocular intolerance scores in our trial (Table 4) were 13 for DPE against 14 for EPI. We considered that five patients from each group were unable to tolerate their therapy owing to side effects in the long term. As these included the two EPI patients with a shaking reaction, DPE was actually less well tolerated locally. Our findings suggest that DPE may be indicated only in those patients showing idiosyncratic side effects with EPI.

Several short-term investigations[17-20] of timolol and DPE in combination confirm an additive effect. It would seem[20] that adding timolol to DPE has a greater effect than the converse. Thomas and Epstein[21] confirmed this with their work on timolol and EPI in combination. They also confirmed that this additive effect is short lived, due in all probability to changes in B receptor population mediated by the treatment drugs themselves.[22] Their findings agree with those of others,[23,24] and they proposed a 'pulsed' combination regimen, adding timolol episodically to an EPI baseline. It is perhaps unfortunate that the baseline should be EPI rather than timolol because of the former's higher incidence of side effects. Nevertheless, this suggestion merits further consideration, particularly as our results do not favour the adoption of either DPE or EPI as first-line drugs for open-angle glaucoma.

References

1 Wei C, Anderson JA, Leopold I. Ocular absorption and metabolism of topically applied epinephrine and a dipivalyl ester of epinephrine. *Invest Ophthalmol Vis Sci* 1978; **17:** 315–21.

2 Mandell AI, Stentz F, Kitabachi AE. Dipivalyl epinephrine: a new pro-drug in the treatment of glaucoma. *Ophthalmology* 1978; **85:** 268–75.

3 Kaback MB, Podos SM, Harbin TS, Mandell A, Becker B. The effects of dipivalyl epinephrine on the eye. *Am J Ophthalmol* 1976; **6:** 768–72.

4 Kerr CR, Hass I, Drance SM, Walters MB, Schultzer M. Cardiovascular effects of epinephrine and dipivalyl epinephrine applied topically to the eye in patients with glaucoma. *Br J Ophthalmol* 1982; **66:** 109–14.

5 Podos SM, Ritch R. Epinephrine as the initial therapy in selected cases of ocular hypertension. *Surv Ophthalmol* 1980; **25:** 188–94.

6 Krieglstein GK, Leydhecker. The dose-response relationships of dipivalyl epinephrine in open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1978; **205:** 141–6.

7 Tarkkanen A, Laatikainen L. Dose response analysis of 0·1%, 0·5%, 1% and 2% epinephrine in chronic open-angle glaucoma. *Acta Ophthalmol (Kbh)* 1974; **123:** 47–51.

8 Bischoff P. Erfahrungen mit einem neuen Adrenalinpraparät in der Glaukomtherapie (dipivalyl-epinephrin). *Klin Monatsbl Augenheilkd* 1978; **172:** 565–8.

9 Kass MA, Mandell AI, Goldberg I, Paine JM, Becker B. Dipivefrin and epinephrine treatment of elevated intraocular pressure. A comparative Study. *Arch Ophthalmol* 1979; **97:** 1865–6.

10 Kohn AN, Moss AP, Hargett NA, Ritch R, Smith H, Podos SM. Clinical comparison of dipivalyl epinephrine and epinephrine in the treatment of glaucoma. *Am J Ophthalmol* 1979; **87:** 196–201.

11 Azuma I, Hirano T, Utsumi T, Nishida T. Effects of dipivalyl epinephrine (DPE) on intraocular pressure and pupil. *Nippon Ganka Gakki Zasshi* 1977; **8:** 1036–44.

12 Wang BC, Bloxham DD, Goetz KL. Effect of dipivalyl derivatives of catecholamines on cardiovascular function in the conscious dog. *J Pharmacol Exp Ther* 1977; **203:** 442–8.

13 McClure DA. The effect of a pro-drug of epinephrine (dipivalyl epinephrine) in glaucoma—general pharmacology, toxicology, and clinical experience. In: Higuchi T, Stella V, eds. *Pro-drugs as novel drug delivery systems.* Washington, DC: American Chemical Society, 1975; **14:** 224–35.

14 Anderson JA. Systemic absorption of topical ocularly applied epinephrine and dipivefrin. *Arch Ophthalmol* 1980; **98:** 350–3.

15 Yablonski ME, Shin DH, Kolker AE, Kass M, Becker B. Dipivefrin use in patients with intolerance to topically applied epinephrine. *Arch Ophthalmol* 1977; **95:** 2157–8.

16 Theodore J, Leibowitz HM. External ocular toxicity of dipivalyl epinephrine. *Am J Ophthalmol* 1979; **88:** 1013–6.

17 McGuinness R, Frumar KD. Timolol and dipivalyl epinephrine combination therapy. *Aust J Ophthalmol* 1982; **10:** 179–82.

18 Ober M, Scharrer A. Timolol und adrenalindipivalat bei der Behandlung des erhohten intraocularen Druckes. *Graefes Arch Clin Exp Ophthalmol* 1980; **213:** 273–81.

19 Knupp JA, Shields MB, Mandell AI, Hurvitz L, Spaeth GL. Combined timolol and epinephrine therapy for open angle glaucoma. *Surv Ophthalmol* 1983; **28:** 280–4.

20 Keates EU, Stone RA. Concomitant administration of dipivefrin and timolol maleate: safety and effectiveness. *Am J Ophthalmol* 1981; **91:** 243–6.

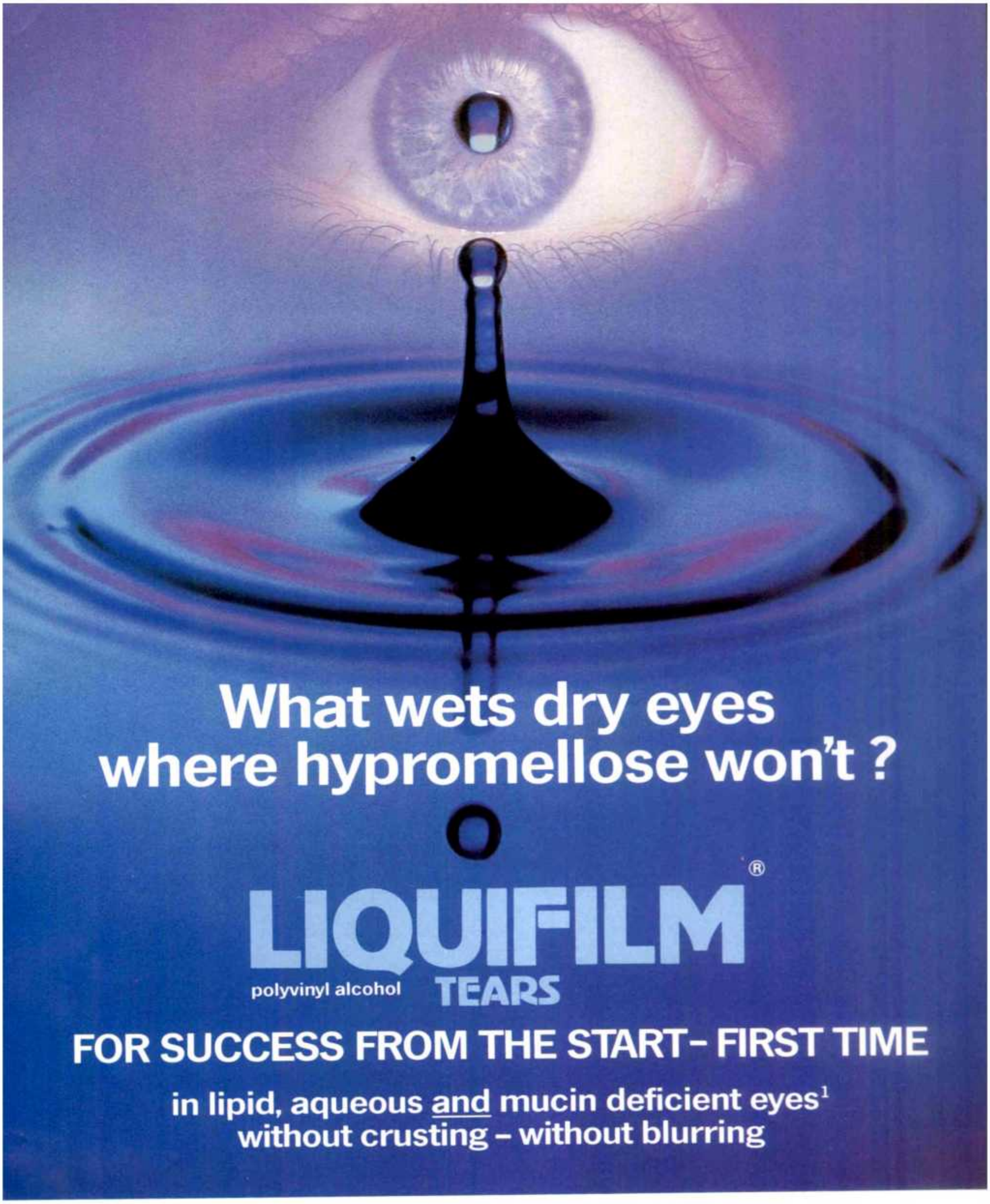
21 Thomas JV, Epstein DL. Study of the additive effect of timolol and epinephrine in lowering intraocular pressure. *Br J Ophthalmol* 1981; **65:** 596–602.

22 Neufeld AH, Zawistowski KA, Page ED, Bromberg BB. Influences on the density of beta adrenergic receptors in the cornea and iris-ciliary body of the rabbit. *Invest Ophthalmol Vis Sci* 1978; **17:** 1069–75.

23 Goldberg I, Ashburn FS, Palmberg PF, Kass MA, Becker B. Timolol and epinephrine—a clinical study of ocular interactions. *Arch Ophthalmol* 1980; **98:** 484–6.

24 Korey MS, Hodapp E, Kass MA, Goldberg I, Gordon M, Becker B. Timolol and epinephrine. Long-term evaluation of concurrent administration. *Arch Ophthalmol* 1982; **100:** 742–5.

Accepted for publication 15 April 1987.



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Reference 1. Kralian J M. American Journal of Optometry and Physiological Optics 1986; **63** (No. 4): 304-308

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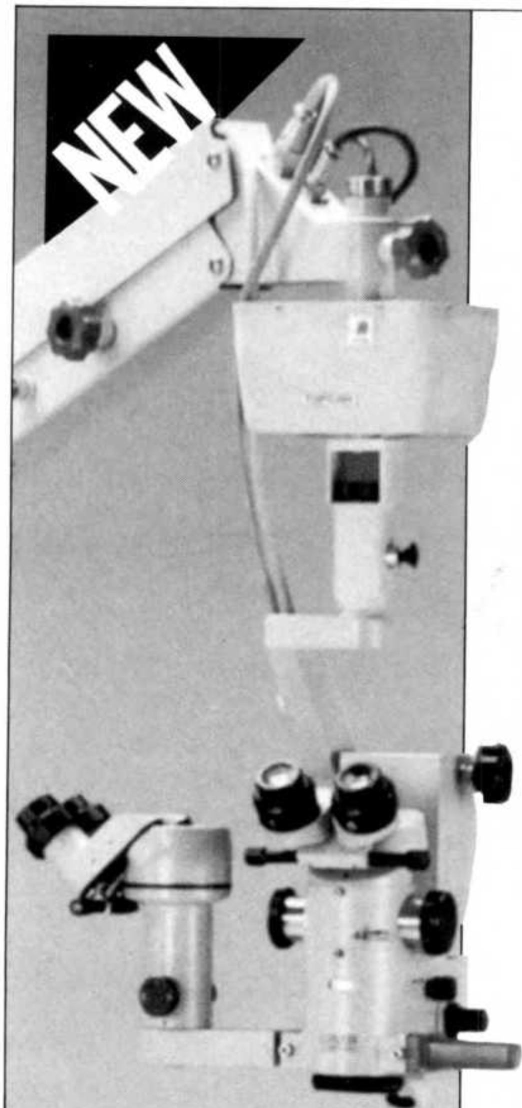

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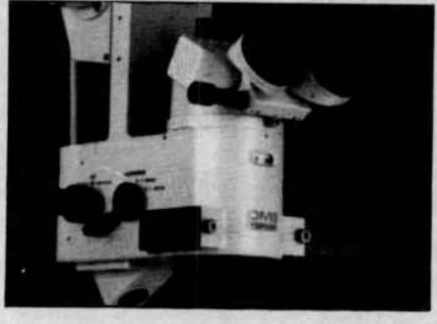

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British Journal of Ophthalmology, 1988, 72, 469–472

A study of the effects of four concentrations of D-timolol, 0·25% L-timolol, and placebo on intraocular pressure on patients with raised intraocular pressure

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From the Manchester Royal Eye Hospital

SUMMARY The intraocular pressure lowering effect in 30 patients with raised intraocular pressure and open angles following a single application in a randomised double-masked fashion of four concentrations of D-timolol (0·25%, 0·5%, 1·0%, and 2·0%), 0·25% L-timolol, and placebo are presented. The percentage reduction in intraocular pressure after four hours following single-drop instillation range from 20% to 25% in the D-timolol group, 32% in the L-timolol group, and only 8% in the placebo group of treated eyes.

The role of L-timolol (that is, the S-enantiomer of timolol) in the treatment of glaucoma is well established.[1-3] The success of L-timolol can be attributed to its relatively long duration of action, the minimal development of tolerance, and lack of membrane stabilising (local anaesthetic) activity. However, L-timolol, being a non-selective β-adrenergic blocking agent, must be used with caution in patients with known contraindications to the systemic use of β-adrenergic receptor blocking drugs. These include bronchial asthma, sinus bradycardia and greater than first degree heart block, and cardiogenic shock. Any systemically absorbed drug following topical administration may affect extraocular β-adrenergic receptor systems in the same patients.

The R-enantiomer of timolol (D-timolol) is also a non-specific β-adrenergic blocker, but its potency as a β-blocker is substantially less than that of L-timolol.[4] D-Timolol has only 3% of the potency of L-timolol in blocking the isoproterenol-induced synthesis of adenosine 3–3, 5, monophosphate in iris-ciliary body preparations.[5] In water loaded pigmented rabbits both stereoisomers blunt the peak increase in intraocular pressure and also reduce its down phase, though L-timolol is more effective.[5] D-Timolol is about one-third as potent as timolol in displacing ^{3}H-dihydro-alprenolol binding to iris-ciliary body tissue, reducing aqueous humour formation, and lowering intraocular pressure of α chymotrypsin hypertensive eyes.[6] In contrast the R-enantiomer is 50–90 times less potent than timolol in antagonising the effects of isoproterenol on pulmonary and atrial β-adrenergic receptors[6] and may be effective in lowering intraocular pressure in man at concentrations which may reduce the systemic side effects associated with peripheral β-adrenergic blockade. D-Timolol has been shown to produce a significant lowering of intraocular pressure following single-drop application in patients with ocular hypertension.[7]

The present study was undertaken to compare the effects on raised intraocular pressure of a single application of four concentrations of D-timolol (0·2%, 0·5%, 1·0%, and 2·0%) with 0·25% L-timolol and placebo in patients with raised intraocular pressures and open angles.

Patients and methods

Patients with raised untreated, symmetrical (no more than 5 mmHg difference in intraocular pressure between eyes) intraocular pressures (of 22 mmHg in each eye or higher by Goldmann applanation tonometry) and open angles, between the ages of 18 and 75, were considered for inclusion in the study. Patients suffering from, or with a history of, cardio-

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vascular disease or constrictive airways disease, active corneal disease or corneal scarring, previous ocular surgery, or receiving concomitant systemic medication affecting intraocular pressure, including β-blocking drugs and clonidine, or taking adrenergic augmenting psychotropic drugs such as monoamine-oxidase inhibitors or tricyclic antidepressants were excluded from the study.

Thirty patients gave their informed written consent to take part in the trial (and were free to remove themselves from the trial without explanation at any time). Each of the 30 patients received two of the six possible treatments. The allocation of treatments was such that each was given to 10 different patients. Only one eye was treated, and the eye to be treated and the treatment to be received were determined by a random allocation schedule. Each treatment was delivered from identical 5 ml ocumeters containing one of the following six compounds; 0·25% D-timolol, 0·5% D-timolol, 1·0% D-timolol, 2·0% D-timolol, 0·25% L-timolol, and placebo to match (vehicle of D-timolol).

All intraocular pressure reducing medications were washed out for at least two weeks. Within this period all patients had, before treatment, history taken and examination made to ensure that they satisfied admission and exclusion criteria.

Immediately prior to treatment the resting heart rate and blood pressure were measured in all 30 patients after they had been sitting for four minutes. The visual acuity, pupillary size, and results of an external ocular examination followed by an initial applanation intraocular pressure were recorded for both eyes. The first of the randomly assigned drops was instilled into the conjunctival sac of one randomly selected eye. All examinations were repeated at one, two, and four hours after treatment.

Each patient returned two weeks later to receive the second treatment in the same eye as the first treatment. No ocular treatment was allowed during the period between the first and second treatment days. Examinations for the second treatment day followed the same schedule as for the first day. Any subjective side effects following topical instillation of any of the treatments were noted.

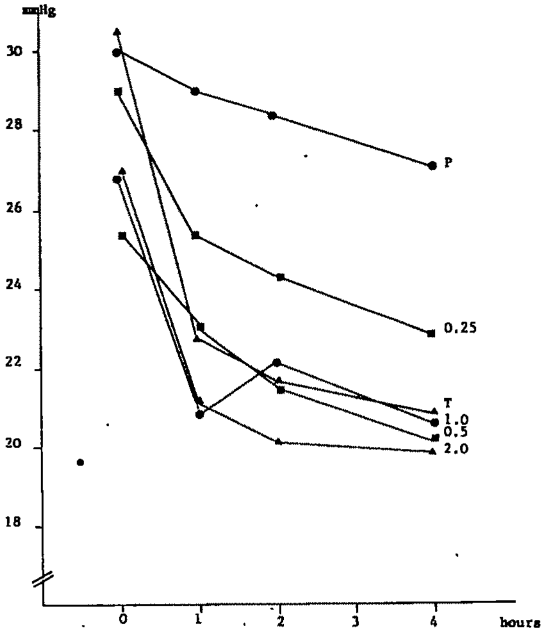

Fig. 1 *Mean IOP: treated eyes. P=placebo. 0·25= D-timolol 0·25%. T=L-timolol 0·25%. 1·0=D-timolol 1%. 0·5=D-timolol 0·5%. 2·0=D-timolol 2%.*

Results

All 30 patients completed the study. The mean IOP in the treated eyes at the studied time points are shown in Fig. 1. The results were compared by single classification analysis of variance. The mean starting intraocular pressures (as shown in Table 1) were statistically similar in each treatment group ($p>0·05$) and ranged from 25·4–30·5 mmHg. Four hours following the administration of the eye drops the intraocular pressure had fallen by varying amounts according to the treatment used (Table 1). Placebo and 0·25% D-timolol did not produce a significant reduction in intraocular pressure. However, 0·5, 1%, and 2% D-timolol and 0·25% L-timolol did all produce a significant reduction in intraocular pressure four hours after treatment in comparison with placebo (variance ratio 2·6; $p<0·05$). These reductions in intraocular pressure did not differ significantly from one another. Fig. 2 and Table 2 show the mean change in intraocular pressure in the treated eyes over time following single-drop instillation of each treatment.

The initial intraocular pressures in untreated eyes were similar in each group (variance ratio 1·5%;

Table 1 *Initial and four-hour mean IOPs and percentage IOP reduction over four hours—treated eyes*

Treatment	*n*	*Starting mean IOP*	*SD*	*Final mean IOP (4 hours)*	*SD*	*IOP Reduction % over 4 hours*
R-timolol (0·25%)	10	29·00	6·8	22·8	6·2	19·42
R-timolol (0·5%)	10	25·4	3·44	20·0	4·4	20·92
R-timolol (1·0%)	10	27·0	4·2	20·6	5·1	23·97
R-timolol (2·0%)	10	27·0	5·4	19·9	4·8	25·34
L-timolol (0·25%)	10	30·5	5·5	20·7	6·7	32·89
Placebo	10	30·2	7·1	27·1	5·7	8·98

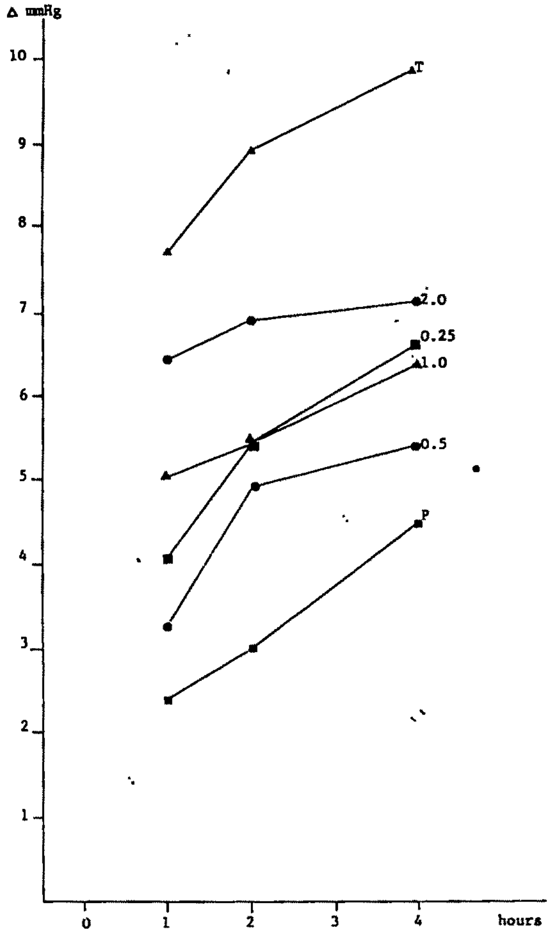

Fig. 2 *Mean fall in IOP: treated eyes. P=placebo. 0·25=* *D-timolol 0·25%. T=L-timolol. 1·0=D-timolol 1%. 0·5=D-timolol 0·5%. 2·0=D-timolol 2%.*

Table 3 *Initial and four hour mean IOPs and percentage IOP reduction over four hours—untreated eyes*

Treatment	*n*	*Starting mean IOP (mmHg)*	*SD*	*Final (4 hours) IOP mmHg*	*SD*	*IOP Reduction %*
R-timolol (0·25%)	10	29·00	5·4	25·9	5·93	8·51
R-timolol (0·5%)	10	27·2	4·2	22·9	3·75	15·53
R-timolol (1·0%)	10	28·5	4·93	25·2	4·69	11·05
R-timolol (2·0%)	10	28·1	4·7	26·1	3·7	6·49
L-timolol (0·25%)	10	31·9	4·04	26·1	3·87	18·08
Placebo	10	31·8	6·68	27·3	5·77	13·79

p>0·05) ranging from 27·20 to 31·90 mmHg (Table 3). The pretreatment mean intraocular pressures for each group of 10 untreated eyes were the same or slightly higher (NS) than the treated fellow eyes. The mean intraocular pressures in the untreated eyes for each treatment group were all lowered four hours after treatment (Table 3). No significant difference could be detected in the untreated eyes between treatments or between treatment and placebo. Any difference in percentage reduction of intraocular pressure between groups in the untreated eyes appeared to be random.

There were no significant differences in blood pressure, pulse, or pupil size between the different treatment groups and placebo at four hours in comparison with the pretreatment state. No subjective side effects were reported.

Discussion

Even allowing for the fact that the mean pretreatment IOPs were slightly though not significantly lower for D-timolol 0·5%, and less so for the D-timolol 1% and 2%, our results confirm that D-timolol concentrations of 0·5%–2% were effective in lowering an elevated intraocular pressure following single-drop application. These reductions were comparable to the reduction produced by 0·25% L-timolol following single-drop application. The percentage fall in IOP for the 0·25% L-timolol was greater than the D-timolol concentrations tested, though not significantly so. The slightly higher initial IOP for the 0·25% L-timolol group makes it difficult to make a completely reliable comparison on these data. The ocular hypotensive effect lasted throughout the period of the study (four hours).

The results of the studies by Share *et al.*[6] indicate that D-timolol lowers intraocular pressure by the same mechanism of action as timolol. However, in extraocular tissues D-timolol is considerably less potent than L-timolol in blocking β-adrenergic receptors.[6,8] This implies that the R-enantiomer may represent an ocular-selective antiglaucoma effect.

Table 2 *Mean differences in IOP (mmHg) (SD)—treated eyes*

Time from instillation	*D-Timolol 0·25%*	*D-Timolol 0·5%*	*D-Timolol 1%*	*D-Timolol 2%*	*L-Timolol 0·25%*	*Placebo*
1 hour	4·1 (1·74)	3·3 (1·68)	5·1 (1·78)	6·4 (1·92)	7·7 (1·99)	2·4 (1·4)
2 hours	5·4 (2·29)	4·9 (1·76)	5·4 (1·97)	6·9 (2·1)	8·9 (2·29)	3·0 (1·47)
4 hours	6·6 (2·54)	5·4 (2·04)	6·4 (1·84)	7·1 (2·25)	9·8 (2·09)	4·5 (1·65)

D-Timolol may act on a population of ocular β-adrenergic receptors which show relatively poor stereo selectivity. If studies on respiratory and cardiac function effects of R-timolol confirm the animal and tissue study data, there will be clear clinical advantages to be gained from the use of this more ocular-selective enantiomer.

This study was supported by a grant from Merck, Sharp and Dohme. We thank Carole Page for her help in preparing the manuscript.

References

1 Katz IM, Hubbard WA, Getson AJ, Gould AL. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. *Invest Ophthalmol Vis Sci* 1976; **15**: 489–92.

2 Zimmerman TJ, Kaufman HE. Timolol—beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977; **95**: 601–4.

3 Mills KB. Blind randomised non-crossover long-term trial comparing topical timolol 0·25% with timolol 0·5% in the treatment of simple chronic glaucoma. *Br J Ophthalmol* 1981; **67**: 216–9.

4 Wasson BK, Gibson WK, Stuart RS, Williams HWR, Yates CH. Beta-adrenergic blocking agents 3-(3-substituted-amino-2-hydroxy-propoxy)-4-substituted-1,2,5-thiadiazoles. *J Med Chem* 1972; **15**: 651.

5 Liu JH, Bartels SP, Neufeld AH. Effects of L- and D-timolol on cyclic AMP synthesis and intraocular pressure in water-loaded, albino and pigmented rabbits. *Invest Ophthalmol Vis Sci* 1983; **24**: 1276–82.

6 Share NN, Lott VJ, Gautheron P, *et al.* R-enantiomer of timolol—a potential selective ocular antihypertensive agent. *Graefes Arch Clin Exp Ophthalmol* 1984; **221**: 234–8.

7 Keates EU, Stone R. The affect of D-timolol on intraocular pressure in patients with ocular hypertension. *Am J Ophthalmol* 1984; **98**: 73–8.

8 Chiou GCY. Effects of D-timolol on intraocular pressure, heart rate, cardiac contractibility and tracheal muscle function. *Curr Eye Res* 1983; **2**: 507–10.

Accepted for publication 2 April 1987.

British Journal of Ophthalmology, 1988, **72**, 473–474

Slit-lamp photography made easy by a spot metering system

P T KHAW AND A R ELKINGTON

From Southampton University, Southampton Eye Hospital

SUMMARY The use of a standard 35 mm camera with a spot metering system to take slit-lamp photographs is described. This system is mounted on a standard Haag-Streit slit-lamp and can be used with good results even by inexperienced operators.

Ophthalmology lends itself to photography. However, the cost of a dedicated slit-lamp camera and the technical difficulties involved deter many ophthalmologists from taking slit-lamp photographs. What is needed is a system that is (1) inexpensive; (2) based on photographic apparatus readily available; (3) compatible with a standard slit-lamp; (4) as easy to use as a standard automatic camera, without any complicated settings.

A system has previously been described by Thaller[1] that fulfils the first three of these criteria. His system consisted of a standard 35 mm camera and standard f 1.8 aperture lens mounted on a ×10 Haag-Streit eyepiece by a simple adaptor. To take a photograph the camera and lens are mounted on the eyepiece, which is then inserted into the slit-lamp. Focusing is achieved by moving the slit-lamp backwards and forwards, and illumination is provided as usual by the slit-lamp light source.

However, this leaves the correct exposure to be determined by altering the speed of the shutter. The shutter speed can be extremely difficult to estimate, even after experience of several hundred photographs with this system. A small difference in slit width or lamp intensity can significantly alter the illumination. This necessitates taking three or more exposures to guarantee one acceptable photograph. The conventional centre weighted metering system of the standard camera cannot be used to automate this procedure. This is because the centre weighted system averages the illumination over the whole picture, whereas slit-lamp illumination varies considerably over the field of view.

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Table 1 *Photographs that can be taken with the system*

Area	*Notes*
Conjunctiva/whole eye, iris	The whole eye can be photographed (wide angle view) if a Hruby lens is used between the slit-lamp and the eye
Cornea: Section	Take reading from centre of slit. To achieve a picture with more than a slit of light surrounded with darkness use the overexposure facility (highlight)
Whole	Wide illumination beam and take exposure reading off centre of picture
Fluorescein	Switch up the lamp voltage to 7·5 V or the shutter speed will probably be too slow
Endothelium	Use endothelial contact lens. Try to angle illumination so that reflections do not enter the metering area or the photograph will end up too dark
Scleral illumination	Decentre beam to illuminate sclera and take reading from actual lesion, e.g., corneal disciform scar
Anterior chamber angle	Use gonioscope normally and take reading from part of picture required. Again, try to avoid reflections into the metered area
Lens: Section/whole	Same technique as corneal section.
Retroillumination	Try to illuminate obliquely so that the meter does not read directly from the slit of light on the lens. The overexposure facility (highlight) can be used to ensure an adequately exposed picture
Fundus disc/post pole	A Hruby lens, 90 dioptre lens, contact lens, three-mirror lens, or panfunduscope can be used. Some type of reflection will always be present in the picture, unlike a fundus camera. However, good pictures can be obtained. Again, oblique illumination helps to avoid inaccurate metering and excessive reflections in the photographs

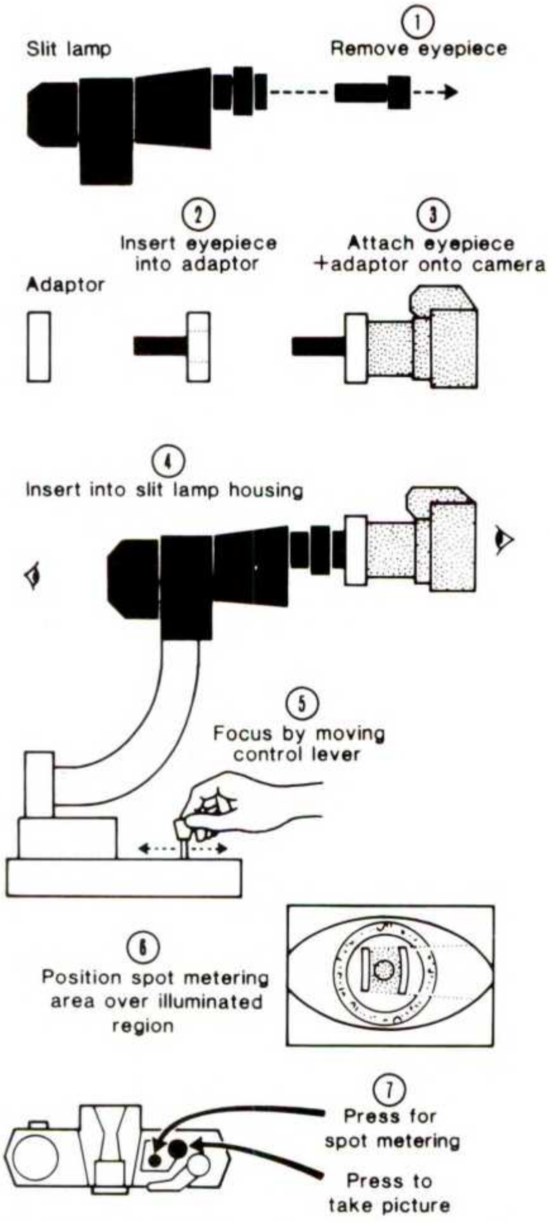

Slit lamp
①
Remove eyepiece
②
Insert eyepiece into adaptor
③
Attach eyepiece +adaptor onto camera
Adaptor
④
Insert into slit lamp housing
⑤
Focus by moving control lever
⑥
Position spot metering area over illuminated region
⑦
Press for spot metering
Press to take picture

Fig. 1 *Procedure for taking slit-lamp photographs with a standard 35 mm camera which has a spot metering facility.*

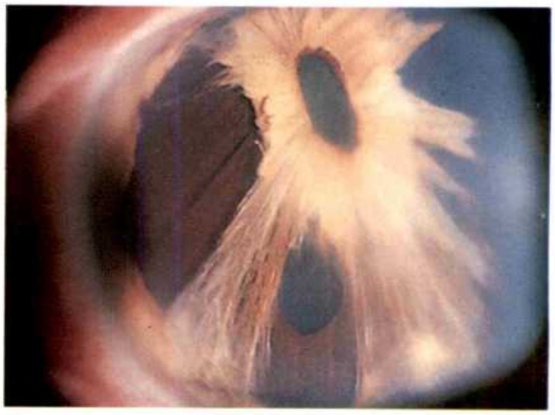


Fig. 2 *Essential iris atrophy and mild corneal oedema. Photograph taken with spot metering at ×16 magnification.*

Several cameras have recently become commercially available on the mass market which have a spot metering system. These take readings from the central 2% of the picture and base exposures on these readings. We used one of these cameras (Olympus OM-4) with a standard f 1.8 lens mounted on a Haag-Streit slit-lamp. The procedure for taking photographs was very simple (Fig. 1). The camera was used to photograph parts of the eye as shown in Table 1. Ophthalmologists with little or no photographic experience found the camera easy to use. They achieved acceptable results even at the first attempt.

The main problem with this system arises when relatively slow shutter speeds are sometimes necessary. This occurs particularly when blue light is used and when pictures are taken by retroillumination. This results in a blurred picture. If the intensity of the slit-lamp is switched up, the patient will not be able to tolerate the enhanced illumination. Initially Kodak Ektachrome Tungsten 160 ASA colour slide film was used, but the use of faster film such as 3M ASA 640 colour slide film helped to overcome many of these problems. Obviously even the most sophisticated metering system in existence cannot cope with all lighting conditions, but the spot metering system could cope with the majority of slit-lamp photographic conditions.

In summary, we are using a relatively inexpensive photographic system for slit-lamp photography that can be easily operated by ophthalmologists with little or no photographic experience. In addition, the camera purchased for this purpose (being a standard 35 mm camera) can also take excellent general photographs.

We thank Mr S Douglas of Olympus Optical Co. (London) for the loan of the OM-4 and Mr Peter Jack for his illustration.

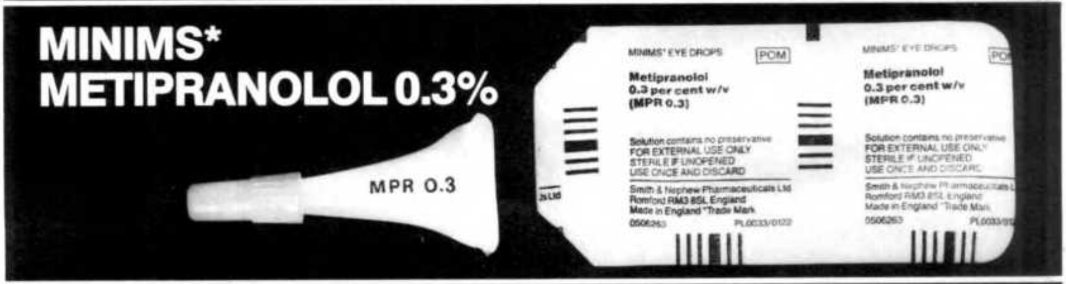
Mr Khaw is in receipt of a 1986 Kodak bursary award.

Reference

1 Thaller VT. An inexpensive method of slit-lamp photography. *Br J Ophthalmol* 1983; **67:** 63–6.

Accepted for publication 27 March 1987.

The only topical ophthalmic beta blocker that is obtainable in 3 strengths. Now available in single dose units, containing no preservative.



PRESCRIBING INFORMATION

Single use, clear, colourless, sterile eye drops. Three strengths are available; 0.1% w/v, 0.3% w/v and 0.6% w/v as metipranolol.

No preservatives are included in the formulation.

USES

Metipranolol is a non selective beta adrenoreceptor blocking agent.

Minims metipranolol is indicated for the treatment of raised intra-ocular pressure. It is particularly suitable for the treatment of patients who are allergic to preservatives, for control of post operative increases in intra-ocular pressure and as an initial test for responsiveness to metipranolol therapy.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop instilled into the affected eye twice daily. Newly diagnosed patients should be treated in the first instance with the 0.1% w/v strength changing to a higher strength if adequate control is not achieved or maintained.

If used as a diagnostic agent before planning a treatment programme then only one drop need be instilled.

In the treatment of post-operative rises in intra-ocular pressure the dosage and frequency should be at the discretion of the physician.

CONTRA-INDICATIONS AND WARNINGS

The use of Minims metipranolol is not recommended in patients with obstructive airways disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Minims metipranolol should only be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block.

Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out.

Intra-ocular pressure should be determined at frequent and regular intervals.

Ophthalmic solutions should only be used in patients fitted with contact lenses at the discretion of the Physician.

PHARMACEUTICAL PRECAUTIONS

Minims should be stored in a cool place (8°-15°C) and should not be exposed to strong light.

LEGAL CATEGORY

POM.

PACKAGE QUANTITIES

Cartons of 20 units, each unit containing approximately 0.5g of solution.

FURTHER INFORMATION

Metipranolol has little or no effect on pupil size or accommodation. Metipranolol is generally well tolerated but some patients may experience slight, transient stinging. Transient headaches have been reported.

PRODUCT LICENCE NUMBERS

Minims metipranolol 0.1% w/v 0033/0121
Minims metipranolol 0.3% w/v 0033/0122
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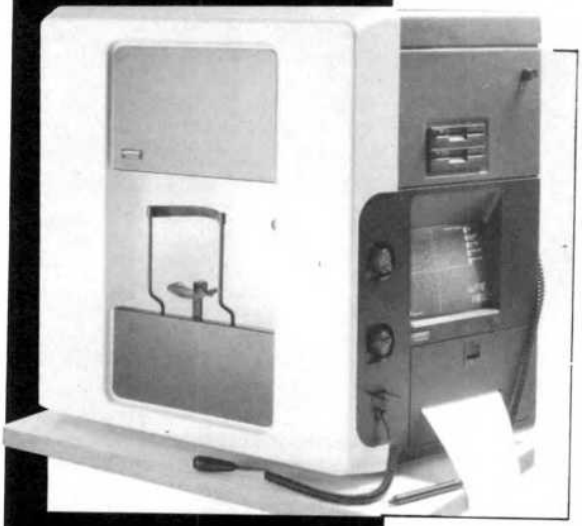

The Humphrey Field Analyzer is an automated, computerised projection perimeter. It has all the standards of the traditional Goldmann and offers a wide variety of screening test patterns and sophisticated threshold-related strategies which enable you to identify the most subtle defects. It also provides you with quantitative data analysis to highlight areas of significance and allow you to easily monitor pathologies.

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British Journal of Ophthalmology, 1988, **72**, 475

Book reviews

The Physiology of the Cornea and Contact Lens Applications. By Hikaru Hamano and Herbert E Kaufman. Pp. 100. £29·00. Churchill Livingstone: Edinburgh. 1986.

It is interesting to note that the two latest books dealing with changes in structure and function of the eye produced by contact lens wear have a similar cover—a photograph of interference fringes produced by varying tear-layer thicknesses on the front surface of a contact lens. Apart from the intrinsic charm of the patterns it also neatly illustrates that the repeated or continuous application of a manufactured appliance to the external eye is producing changes only imperfectly understood. Textbooks dealing with this topic are a comparatively new phenomenon, but a bench mark has been set over the last few years.

Compared with others of this genre the book cannot be considered a success. It would appear that the authors have not formulated an overall plan but have assembled a text from unrelated chapters, producing a book lacking cohesion and form. Furthermore the chapters written by the two authors are at a markedly different intellectual level, one giving essentially a personal account of a long career in contact lens research, the other a simplistic and basic primer on contact lens materials and fitting. For a book with this title there are also some surprising omissions. For example, there is no mention of the effect of contact lens wear on corneal sensation, an area where a large and pertinent literature exists.

In the chapter dealing with the anatomy of the cornea the majority of the illustrations are of the rabbit, no doubt culled from the authors' vast research output on this particular model. There is however a large amount of human material available, and in a 'clinical' book it is surprising it was not used. Although the corneal endothelium is described, the effect of contact wear upon it is not. This has been one of the growth areas of research in the last 10 years, and this omission demonstrates the insularity of the book. Chapter 3, 'Physiology of the cornea and effects of contact lens wear', is a fascinating account of Hamano's research work of the last 20 years. However apart from his own publications no references are given later than 1974, Chapter 4, dealing with the tear film and contact lens wear, quotes only Japanese work, completely ignoring the large American and European literature.

Chapter 5, 'Selection of contact lenses: clinical applications', is written in a question and answer format using a great deal of unscientific terminology—'sucked-on', 'cornea cannot breathe', 'see much more naturally', etc. This suggests that the chapter may originally have been written for an audience without specific ophthalmic training. In addition the statement on page 70 that in cases of nystagmus 'contact lens correction is more appropriate, because the lens remains centred in the optical axis, and asthenopia (eyestrain) is reduced', would not find acceptance in many circles.

For those readers who know the subject the book is of historiographic interest; for those seeking a basic knowledge of the important aspects it cannot be recommended. Its lack of breadth is demonstrated by the fact that of the 77 references cited 39 relate to the work of one of the coauthors. The preface to the book states, 'it is most important that we become knowledgeable about the interactions between the lenses and the cornea and tear film.' Study of this book would bring only limited progress towards that end.

E G WOODWARD

Primary Eye Care in Developing Nations. By Larry Schwab. Pp. 203. £2·50. Oxford University Press: Oxford. 1987.

The 11 chapters start conventionally with 'Form and function,' followed by 'The eye examination.' Then there follow chapters on the main blinding conditions: cataract, blinding infection, malnutrition, glaucoma, and eye injuries. A further chapter deals with other disorders, including onchocerciasis, uveitis, and macular and retinal conditions. Squint is included here. Then there is a chapter devoted to refractive errors.

This volume contains a great deal of valuable practical information, arising from Dr Schwab's extensive experience in several African countries. This is particularly evident in the last two chapters, which deal with 'Appropriate technology' and 'Public health ophthalmology.'

The problem is the uneven treatment in the different sections. The reader gets the impression that the book started out to be a textbook based on the needs of ophthalmic medical assistants (or clinical officers, ophthalmic) in training, and then to widen the readership parts were simplified or abbreviated. The title 'Primary eye care' is therefore misleading. For example, the detailed description of cataract extraction and its complications, which is well done, would not normally be considered as part of primary eye care. Similarly, how to carry out refraction is not a function of primary health care workers, and gonioscopy is certainly not a primary care function. On the other hand the description of anatomy in very elementary terms, though suitable for a health assistant, would not be detailed enough for the trainee ophthalmic assistant or general physician.

There are some unfortunate errors, which detract from the authority of the text. Muscular contraction of the ciliary body causes the lens to become more spherical in accommodation, not to flatten as stated. In the drawings of esotropia and exotropia the light reflexes from the cornea are in the wrong positions. It is also surprising that the experienced reviewers allowed the use of diethyl carbamazine for onchocerciasis to be included without stronger qualification, in view of our present knowledge of the adverse effects on the eye. There is nevertheless a wealth of information in this book and everyone will find something of value. One suspects that in any given training course some of the text will be found to be very useful, other parts to be less relevant.

When it goes into a second edition, as one hopes that it will, there would be an argument for focusing on the needs of one group—the ophthalmic medical assistants—and concentrating on their requirements and the level of detail they require throughout. There would then be a place for a second, much simpler, book addressed to the true primary eye care workers.

GORDON J JOHNSON

Vitamin A Deficiency and its Control. Edited by J CHRISTOPHER BAUERNFEIND. Pp. 530. £74·00. Academic Press: London. 1986.

This multiauthor book is a comprehensive text dealing in detail with vitamin A, its functions, the effects of deficiency, and strategies for the control of vitamin A deficiency.

The first half of the book deals with recent scientific understanding of the biochemistry, physiology, and nutritional aspects of vitamin A and its deficiency. There is objective reviewing of important papers in the fields of the metabolism of vitamin A, relationships between vitamin A and other nutrients, the role of vitamin A in the immune system, vitamin A in pregnancy, and vitamin A and carcinogenesis. For each subject extensive references are given. The text highlights the deficiencies in our knowledge, particularly in regard to the functions of vitamin A, its role in the immune system, and the interrelationship between vitamin A, infections, and child mortality. This section will certainly be of interest and give an excellent reference text to scientists involved in work related to nutrition and particularly vitamin A.

The second and larger section of the book briefly discusses the pathogenesis and clinical aspects of vitamin A deficiency, illustrated with black-and-white photographs, before turning to a comprehensive review of strategies for the control of vitamin A deficiency. Following this are chapters on the control programmes in India, Central America, the Philippines, and Indonesia, showing the different experiences and possible ways in which vitamin A deficiency may be managed at the national level. This second section on the control of vitamin A deficiency will be of great use to those involved in policy and programme planning in the field both of vitamin A deficiency and of other nutritional deficiencies.

With many authors there is a wealth of expert knowledge but also a significant amount of repetition of information. The book is a comprehensive text which seeks to unite the laboratory vitamin A research worker with the programme field officer dealing with vitamin A deficiency in a community. This is a mighty task, and one in which I believe the editor has been largely successful, in putting together this reference text.

ALLEN FOSTER

Ophthalmology Annual 1987. Edited by ROBERT D REINECKE. Pp. 213. £69·55. Prentice-Hall: London. 1987.

This is a very workmanlike book of 206 pages with a large number of references for each section, so there is plenty of secondary reading for the interested ophthalmologist. This is the third volume of *Ophthalmology Annual* and keeps up the good work of the previous two volumes. Selection of material is a skill and the series editor has done well in achieving a balance between esoteric topics and those for a wider general readership.

An account of penetrating keratoplasty and cataract surgery in children forms the opening section. This is a good review article, suitably conservative but possibly over cautious when discussing intraocular lenses in children. The section on visual acuity and cataract surgery will interest most ophthalmologists, as after all it is the basis of much of their daily work. The section describes the various adjuncts to assessing visual function in patients with cataracts—especially important where coexistent ocular disease is present. Equipment such as PAM (potential acuity meter), blue field endoscopy, LIP (laser interferometric acuity), VEP (visual evoked potential), and pattern VEP are described and their place in assessing cataract patients evaluated. The sections on penetrating ocular trauma and on surgical management of hyphaema concentrate mostly on vitreous surgery and surgical treatment of hyphaema respectively. The latter management of hyphaema is perhaps over elaborate. Optic neuritis is an excellent, lucid section with some welcome clinical guidelines such as that 'CT scan should not be used to diagnose optic neuritis; it is used in the evaluation of patients suspected of having optic neuritis for the purpose of helping to eliminate certain other disorders.'

The section on oblique muscle surgery summarises the current views and indication for this type of surgery. The diagrams in this section are less than clear, which is unfortunate, as clear diagrams would have helped the reader greatly. Glare disability at first glance seems an unusual inclusion in this volume, but an excellent section on this subject sets out to examine and quantitate a widely encountered physiological and pathological problem. The historical account of Holladay's experiments on glare is of particular interest, leading to the modern methods of glare testing and alleviating glare. Side effects of drugs immediately captures the interest of ophthalmologists who are constantly asked about ocular side effects. This section is very short and is based on recent documentation from the USA Registry of Drug Induced Side Effects, particularly on systemic effects of timolol, allopurinol cataracts, and chloramphenicol blood dyscrasias.

The section on the current status of refractive surgery is suitably conservative in its approach but optimistic about correcting high refractive errors, especially with epikeratophakia. This section summarises present developments satisfactorily. Cosmetic eye surgery commences with a review of the surgical anatomy and outlines the principles of eyelid surgery. Following this is a description of blepharoplasty in various conditions and age groups. A whole section on diabetic macular oedema may seem excessive, but this last section contributes a precise and careful guide to the treatment of this common condition with emphasis on diabetic control, follow-up examinations, and laser treatment.

This is an eminently readable book, and almost all of it will be of value to practising ophthalmologists whatever their special interest.

JAMES L KENNERLEY BANKES

Auge und Brille: Beiträge zur Optik des Auges und der Brille. By JOSEF REINER. Pp. 205. DM 44·00. Ferdinand Enke Verlag: Stuttgart. 1987.

This book on the eye and spectacles represents an updated revision of the 59th volume in the series of ophthalmic textbooks Bücherei des Augenarztes which has contributed so much to German ophthalmology for the past few years. It is a comprehensive manual on optics and refraction, dealing in detail with the theoretical aspects of the subject and providing useful practical advice on such topics as lens forms and materials.

In several sections the book becomes rather too technical for the ordinary ophthalmologist and is better suited for the optician in training, but the author is to be congratulated on his commonsense approach to what can often be a difficult area.

T J FFYTCHE

Bucherei des Augenarztes. Vol. 109. **Akute Augenerkrankungen Akute Symptome.** Eds. Otto-Erich Lund and Theo N Waubke. Pp. 280. DM 76·00. Ferdinand Enke Verlag: Stuttgart. 1986.

The 109th volume of this series is composed of a collection of articles on acute eye disease and symptoms. This attractive idea of grouping together ophthalmic emergencies with situations where a rapid diagnosis is important succeeds well, and the book can be positively recommended to ophthalmologists.

Chapters include neuro-ophthalmological subjects such as acute loss of vision, acute disc swelling and optic neuritis, headache, eye pain and coma, and acute disturbances of accommodation, visual field, ocular movements, diplopia, vertigo, and colour vision. In addition there are contributions on acute aspects of intraocular haemorrhage, uveitis, keratitis, corneal oedema, glaucoma, hypotony, endopthalmitis, exophthalmos, orbital infections, and lens related problems. The management of most of these emergencies conforms to that practised in Britain, although it is refreshing to see the occasional variation, such as the prescribing of a glass of brandy in the treatment of acute closed-angle glaucoma (supported by the appropriate reference).

Tacked on to the end somewhat surprisingly are two articles on AIDS and radial keratotomy, which, although they do not quite fit into the general scheme of the book, are useful contributions in their own right.

Good editorship has produced a uniformity of presentation with excellent illustrations and diagrams and has kept down the number of unnecessary references, and each chapter, with one exception, carries an English translation of the summary.

This volume provides a useful reference book, not only for ophthalmologists in training but also for those in practice as well.

T J FFYTCHE

Rechtliche Grundlagen der augenärztlichen Tätigkeit. By Berndt Gramberg-Danielsen. Pp. 128. DM 54·00. Enke: Stuttgart. 1986.

This handbook on legal guidelines in ophthalmic practice is produced in the form of a loose-leaf folder divided into sections. Within these are included information and advice on such subjects as the civil rights of the individual patients and ophthalmologists, legal and social rights, industrial medicine, and guidelines on minimal requirements for visual suitability and fitness in various occupations. Certain sections are left empty, presumably to be filled later, and interestingly these include headings on criminal law, professional rights, and scales of charges. Apart from a brief insight into some of the bureaucratic aspects of German ophthalmic practice there is little in this publication to interest the British ophthalmologist, nor is there likely to be, even if the missing sections are filled.

T J FFYTCHE

Clinical Ophthalmology. Edited by Sir Stephen Miller. Pp. 599. £65·00. Wright: Bristol. 1987.

This is an excellent book. It fills a notable gap in the currently available ophthalmic literature by providing a comprehensive and in general up to date review of virtually the entire subject of clinical ophthalmology, and at a reasonable price.

The editor has assembled 23 main chapters by 50 highly respected authors, most of whom are practising ophthalmologists. The main emphasis has been directed towards the clinician, with good supporting chapters on electrophysiology, pharmacology, biochemistry, ultrasound, immunology, low vision, and epidemiology. Most of the chapters are well referenced.

Inevitably in a book of this size there are some weaker chapters, but overall it provides a superb update on current ophthalmic practice. An obvious omission is the lack of a chapter on orbital disease, but this is partly rectified by a very good contribution on radiology and the orbit.

In summary, I can warmly recommend this book to all with an interest in ophthalmology. It is very much a postgraduate text, and a fairly advanced knowledge of the subject is assumed. There are many examples of the 'subtle insights' alluded to by the editor in the preface, and every ophthalmologist will find something of interest here. FRCS candidates will find this book an invaluable adjunct to their reading, while all medical libraries should consider buying at least one copy.

JOHN BEARE

Cosmetic Blepharoplasty: An Illustrated Surgical Guide. By Norman Shorr and Stuart R Seiff. Pp. 85. £22·55. John Wiley: Chichester. 1986.

This book is a basic surgical guide to cosmetic surgery around the eyelids which achieves the authors' stated goal of serving as a 'framework for surgeons learning cosmetic blepharoplasty and as a resource to "finesse in blepharoplasty" for the more experienced surgeon.' The authors' techniques of upper and lower lid blepharoplasty are carefully described, and where these descriptions differ from other recognised techniques the reasons are clearly stated. Interestingly the longest chapter is devoted to eyebrow ptosis, and throughout the book great stress is laid on the importance of considering the whole eyelid and eyebrow region and not just the upper or lower eyelids in isolation. In addition there are chapters on blepharoplasty in the oriental patient and on blepharopigmentation. Though no actual technique is described in any detail for treating blepharopigmentation.

The book is well illustrated throughout with diagrams which make the text easy to follow. Not every surgeon practising cosmetic surgery will agree with all the techniques described, but the book certainly achieves its goal of describing a simple logical set of operations which should give excellent results if carried out as recommended. This makes the book well worth buying for the inexperienced surgeon, while the assessment of the basic characteristics of the whole mid-face and eyebrow region in addition to the eyelids makes it interesting reading for those more experienced.

J R O COLLIN

Eye Injuries: An Illustrated Guide. By ELIZABETH M EAGLING and MICHAEL J ROPER-HALL. Pp. 158. £39·50. Butterworth: Guildford. 1986.

This book provides an excellent overview of a vast subject. It contains much valuable information and advice, drawn from the authors' acknowledged wide experience, on the management of a wide range of ocular injuries. The book is well illustrated by 437 high-quality colour photographs and many additional explanatory line-drawings.

The accompanying text is relatively brief and concentrates mainly on the practical aspects of management. As is perhaps unavoidable with such a large subject, the amount of information given on different topics varies widely. For instance, the first chapter would seem to have been written for medical students, whereas later chapters contain adequate information for specialist management.

This is a highly practical volume, which should be at hand in ever casualty department as well as being an extremely useful update for practising ophthalmologists. Z GREGOR

Glaucoma. Vols 1 and 2. Edited by J E CAIRNS. Pp. 1127. US $169·50. Grune and Stratton: Orlando, Florida. 1986.

The late J E Cairns was a much respected ophthalmologist with a lifelong interest in glaucoma. Those of us who came in contact with him benefited from his wisdom, practical approach to glaucoma, and his sense of humour. In addition to these characteristics he will long be remembered for his advocacy of the guarded sclerostomy in the early treatment of primary open-angle glaucoma. Shortly before his death he completed editing this magnificent two-volume book on glaucoma. Here he has collected together as diverse a group of experts as we are likely to see in a subspecialty book on ophthalmology (14 authors from the United Kingdom and Commonwealth, 10 from the continent of Europe, and nine from the USA). Each writer was asked to write on a subject for which he had had firsthand experience and developed noted expertise. By mixing American, European, and Commonwealth writers in this way he has laid out before us a global view of many aspects of glaucoma. It will be a long time before such diversity of authorship will surface again in this subspecialty.

The two volumes are divided in to seven sections. Volume 1 contains the sections on examination, treatment, and pathological physiology, while volume 2 has diagnosis and therapy of closed-angle, open-angle, congenital, and secondary glaucomas. Each section contains a varying number of chapters, so that on occasion a pleasing overlap of subjects involving different approaches may be seen. Chapter writers are allowed to bring the warmth of their personal experience rather than the cold draught of a straightforward literature review (as is so often seen in modern ophthalmic texts) to their contributions. For this reason the book adds much needed icing to the cake of a straightforward textbook. It should be read by all those interested in the subject and referred to by fellowship candidates coming up to that particular exam. John Cairns has given us a magnificent book which will stand proudly on my bookshelf for many years to come. ROGER A HITCHINGS

Laboratory Diagnosis of Ophthalmology. Edited by ZEYNEL A KARCIOGLU. Pp. 268. £60·00. Macmillan: Basingstoke, Hants. 1987.

Dr Karcioglu and his team of contributors adopt a novel approach in this most recent addition to the growing literature on ophthalmic pathology by seeking to inform the practising ophthalmologist about the range of investigative procedures the laboratory has to offer and how to go about getting the best results. As such it is a worthy aim and the book deserves to succeed.

The opening chapters consider the histological diagnosis of eyelid, conjunctival, and orbital disease and of intraocular tumours, with special reference to the techniques of biopsy and examination, while subsequent chapters indicate the diagnostic potential of immunohistochemical staining methods, exfoliative and aspiration cytology, and electron microscopy. Then follow three chapters on microbiological diagnosis. Laboratory tests in the diagnosis of uveitis, of dysthyroid eye disease and of neuro-ophthalmological states come next. Also included are sections on the overall application of biochemical tests and on ocular involvement in haematological disorders.

I like the book because it takes the wide view of ophthalmic pathology as a subject not confined to histopathology, because it draws together a great deal of information not readily found elsewhere (did you know, for instance, that the potassium content of the vitreous is the single most accurate determinant of the time of death?), and because in general it is extremely sound and well written.

And yet, although I have said that it deserves to succeed, I am not sure that it will. It could fall between two stools. Sadly, much of the text could be seen as being unnecessary for most clinical ophthalmologists, these being the ones to whom the book is primarily addressed, particularly when it considers the detailed interpretation of the various tests. Such activity might be regarded as the province of the laboratory workers performing the tests, and indeed, I suspect that the latter may find the book of at least equal value, provided they can be persuaded to overlook some of the more basic parts which for them will almost certainly be redundant. This said, I suggest it should find a place in every laboratory providing an ophthalmic pathology service and in every eye department wishing to make more effective use of its laboratory facility. ALEC GARNER

Glaucomes Secondaires: Actualities sur le Glaucome. Edited by R ETIENNE. Pp. 186. 280 F. SIMEP: Paris. 1986.

This slim volume contains 17 papers which were presented at a symposium and a round table discussion which took place there. All but two of the authors were French. The papers are mainly review articles covering various types of secondary glaucoma and as such cover material already published. Although this material is not necessarily new, some of the views expressed may be new to readers in the United Kingdom, for instance, the 'allergic' theory which lies behind the cause of the Posner-Schlossmann syndrome. The volume concludes with a round table discussion on the use of laser for the treatment of open-angle glaucoma. All the papers are in French.

ROGER A HITCHINGS

Visual Optics and Refraction: A Clinical Approach. 3rd Edn. By David D Michaels. Pp. 564. £64·00. Blackwell: Oxford. 1985.

This is the third edition of a substantial work, and within it can be found much valuable information about the optical states of normal and abnormal eyes and how they are dealt with. But surrounding this valuable information is a great deal of matter whose relationship to the subject of refraction may be questioned. The relevance of the pathology of senile macular degeneration is doubtful, for example, and rather more space is devoted to the subject of squint and amblyopia than is perhaps appropriate. Even in purely optical matters one is surprised to find a modern text making no reference at all to the work on accommodation by Fisher.

Again, the expectations of the results of refraction are raised somewhat high by the suggested causes for failure to obtain a 20/20 result. Aneisokonia is discussed without a true perspective of its present day importance, and this is reflected in the fact that nothing new is referred to on aneisokonia during the last 10 years at least. There is some lack of correlation between the subject of objective and subjective refraction. It is rather as if the reader is expected to know quite a lot about the subject before tackling this work. Perhaps in the United States the way retinoscopy is recorded differs from that on this side of the Atlantic, but one is surprised by the fact that in a book on refraction there is nowhere to be seen the characteristic cross with which we record the findings of retinoscopy, and on this matter the use of the terms 'gross' and 'net' retinoscopy is unfamiliar.

On some of the newer topics the work is helpful, for example, on the available automatic refracting machines and in the section on pseudophakia and on surgery for the ametropias. From these standpoints at least the book deserves a place as a reference source. J D ABRAMS

A Practical Guide to Cataract and Lens Implant Surgery. By R S Bartholomew. Pp. 72. £22·00. Churchill Livingstone: Edinburgh. 1987.

Here is a pleasing monograph concerned with modern extracapsular cataract extraction with the insertion of posterior chamber intraocular lenses. This must be the first book I have seen on the subject which does not attempt to be all things to all surgeons. It has specific aims of dealing with a single subject sensibly and thoroughly, and the book reaches these aims very satisfactorily. The text is straightforward and is illustrated with helpful monochrome line drawings by the author.

Such a volume can be of immense help to ophthalmologists in surgical training and to more senior colleagues faced with the prospect of having to adjust their accustomed surgical techniques to current requirements. The book details the simplicity of this form of surgery and gives careful guidance on the avoidance and the management of common difficulties.

ARTHUR D McG STEELE

Hearing by Eye: The Psychology of Lip-Reading. Eds. Barbara Dodd and Ruth Campbell. Pp. 268. £19·95. Lawrence Erlbaum: London. 1987.

To one who is amazed by the incredible skill of lip-readers or who admires the rare skills of a ventriloquist, this book is a must. Although it will be of greater interest to those in the audiology and allied professions, there are some parts of the book which will be worth while for the ophthalmologist as well. There is a very interesting chapter on the development of phonology in the blind child which outlines the importance of vision in learning to speak, blind children being slower in most areas.

Most of the book comprises chapters by various distinguished psychologists working in the area of speech, language, and phonology, and, while they are a most interesting and useful (according to my paediatric audiologist colleague) collection, it is not likely to be more than glanced at by ophthalmologists and related specialists.

DAVID TAYLOR

Recognizing Patterns of Ocular Childhood Diseases. By Leonard B Nelson, Gary C Brown, Juan J Arentsen. Pp. 187. £45·60. John Wiley: Chichester. 1985.

This excellent little book is a rather novel approach to teaching paediatric ophthalmology to the new resident and, as the authors describe them 'The practicing Ophthalmologist'. Each pair of pages is linked with text on the left and photographs on the right. Subjects are treated with a broad brush, but there is a surprising amount of detail. In fact anyone who is a beginner at paediatric ophthalmology with its totally different set of pathologies could not do better than to look through this book. Useful references are given at the end of each section, and strabismus is given the 20 or so pages out of 187 that its social significance as a cause of visual handicap deserves.

Substantial areas are not covered, but that is quite understandable in a book of this type which complements the use of a larger text. It is to be warmly recommended to residents starting their paediatric ophthalmology training and others with a new interest in the subject.

DAVID TAYLOR

Peripheral Iridectomy: Surgical, Argon, YAG. By Arthur S M Lim. Pp. 86. US$ 40·00. PG Publishing: Singapore. 1987.

This is a small, concise, easily read book liberally illustrated with excellent colour photographs by an author of international repute. There are chapters discussing the indications for peripheral iridectomy, techniques including ab externo, clear cornea, argon laser, and YAG iridotomy, and complications of these procedures. As of any small didactic book, it is easy to quibble about aspects of surgical technique and certain statements. Most experienced YAG iridotomists would not be so cautious about enlarging the iridotomy and would be worried about leaving some of the ones pictured so small. It is unfortunate that the pros and cons of each technique, with their incidence of complications, are not more clearly defined. However, I would have no hesitation in recommending this book for ophthalmologists in training. J JAGGER

Toxicology of the Eye. 3rd Edn. By W. MORTON GRANT. Pp. 1083. US$ 125·00. Charles C. Thomas: Springfield, Illinois. 1986.

There can be few ophthalmologists who have not at some time or other searched the pages of this classic manual of ocular toxicology. Indeed, the dishevelled condition of previous editions to be found in any ophthalmic library speaks for itself. Encyclopaedic in its scope and unrivalled as a reference source, the many distinctive and endearing qualities have more than justified the eminence of this work in the ophthalmic literature.

Updating a work of this nature undoubtedly presents a formidable and painstaking task which the author has accomplished admirably by condensing much of the older literature to make way for new material. The original format and style of the text are unchanged, bearing the personal stamp of the author with the inclusion of many original and useful personal observations. The text is divided into four sections including an introductory outline of the toxic effects of drugs on the eyes and vision arranged on an anatomical basis. From Acacia to Zyklon, the alphabetical listing of individual agents is remarkably comprehensive and provides a description of the local as well as systemic adverse reactions where applicable. Drugs are listed under their generic names but with reference to commonly used proprietary preparations. The dual referencing system can on occasions be somewhat cumbersome, with current and major references appearing at the end of each synopsis together with a bibliography of numbered references for the complete text immediately following the index. The third section contains an excellent summary of the contemporary treatment of chemical burns of the eyes. The fourth section is given over to a brief synopsis of methods used in the evaluation of ocular drug toxicity. There is an exhaustive index that allows easy cross referencing.

A considerable volume of new material has been incorporated, for example botulinum A toxin, viscoelastic materials, current antiproliferative agents, the toxicity of intravitreal antibiotic therapy, and the side effects of beta blocking agents to name but a few. Inevitably, pharmacological data of this type rapidly become outdated, and one must therefore look to national registries of drug induced ocular side effects for additional information. Equally, it is not surprising to encounter a few minor omissions: for example, there is no mention of the inflammatory effects of photochromic glass retained within the eye or the effects of methylisocyanate as dramatically witnessed in the Bhopal incident.

With the publication of the third edition this book remains the most authoritative and incomparable work on ocular toxicology. Whether it is the occasional urgently needed reference or the gentle browse, the mine of fascinating information provides enjoyable and compelling reading. It goes without saying that a copy of this book should always be to hand in any accident and emergency department and all ophthalmic libraries. R COOLING

Notes

Ophthalmic photographers

An International Conference on Ophthalmic Photography will be held at Singapore on 12–15 March 1990. Details from Lawrence M Merin, RBP, Meeting chairman, c/o Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin, Houston, Texas 77030, USA.

American Academy of Ophthalmologists

The 92nd Annual Meeting of the American Academy of Ophthalmology will take place on 8–12 October 1988 at the Las Vegas Convention Center, Las Vegas, Nevada, in the United States. Further information from Meetings Department, American Academy of Ophthalmology, PO Box 7424, San Francisco, CA 94120-7424, USA.

Association for Eye Research

The twenty-ninth meeting of the AER will be held in Albena, Bulgaria, on 25–29 September 1988. Further information from the Programme Secretary, Dr John Tiffany, Nuffield Laboratory of Ophthalmology, Walton Street, Oxford OX2 6AW. Deadline for abstracts is 1 May 1988. The AER Publication Award will be made at this meeting for the best paper in any language, by either members or non-members of AER, published in the 12 months preceding the meeting. Eligible authors must be under the age of 35. In the case of multiauthored papers the award will be made to the main author, and the entry must be accompanied by a statement signed by each author, indicating who this is. The work described must relate to the eye and be original or based on a previously evolved technique or method. Nominations (eight reprints or eight copies of the manuscript accepted for publication) must be made through a member of the AER to the General Secretary: Professor Martin Reim, Abtlg. Augenheilkunde, Med. Fakultät der RWTH Aachen, Klinikum, Pauwelsstrasse, D-5100 Aachen, West Germany, not later than 1 July 1988.

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Typesetting by Bedford Typesetters Ltd., Bedford, England. Printed by Paramount Printing Co. Ltd., Hong Kong

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ASTM CODEN BJOPAL 72 (6) 401–480 (1988)

ISSN 0007-1161

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